THE EFFECTS OF MORPHINE UPON THE CENTRAL CONTROL OF RESPIRATION

by

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Thesis presented for the Degree of Doctor of Philosophy of the University of Edinburgh in the Faculty of Medicine

6th May, 1966

KEY TO FIGURES

INTRODUCTION

In two outstanding respects morphine and related drugs are unique among pharmacological agents. First, they exert a powerful and specific effect upon the perception of pain of all types and, secondly they reliably and predictably depress respiration. There is no other family of drugs with strictly comparable effects. In their respiratory depressant effects, particularly, they stand alone. These two properties - analgesia and respiratory depression - appear in some way to be linked, and, as yet, analgesic members of the group which are devoid of significant respiratory depressant properties are not known (Eckenhoff and Oech, 1960).

Another interesting property of this group of drugs is the development of tolerance, with repeated administration, to certain of their important pharmacological effects, and their liability to cause addiction and dependence under certain conditions. In the human, following continued administration, maximum tolerance develops to their most important clinical effects, namely, narcosis, analgesia and respiratory depression (Reynolds and Randall, 1957).

In ordinary clinical practice, the respiratory depressant properties of morphine and related drugs constitute a more serious limitation to their use than the development of tolerance or the liability to addiction. Despite this, there are surprisingly little quantitative data on the respiratory effects of morphine in man. Further, although morphine has been used for a very considerable period of time in the treatment of acute left ventricular failure, only occasional studies have appeared in which measurements of the effects

of the drug in this or other types of heart failure have been reported. Such observations have, in general, been rather incomplete, and there is, as yet, no satisfactory hypothesis which would account for the beneficial effects of the drug in this condition.

A further point of interest is the comparative rarity of reports, in the modern literature, of deaths or serious mishaps following the therapeutic use of a drug which so regularly depresses respiration. The dangers of using this drug in bronchial asthma, in cor pulmonale, in pulmonary emphysema and in patients suffering from thoracic deformities with impaired pulmonary ventilation are, of course, well documented (Katz and Chandler, 1948; Roussak, 1951; Samuelsson, 1952; Wilson, Hoseth and Dempsey, 1954). With a few other exceptions (Jeghers and Brick, 1950) the clinical use of morphine would seem, from the absence of reports to the contrary, not to carry serious hazards. Notwithstanding, it seems legitimate to enquire whether the respiratory depressant properties of the drug does involve, in actual clinical practice, a measurable risk which might be precisely evaluated.

On the whole, the published literature on morphine has been more concerned with studies bearing on the problem of drug addiction and with the evaluation of the newer synthetic analgesics and opiate antagonists. Usually, the presentation of respiratory data has been incidental to these other objectives.

It seems a reasonable surmise that a drug with the remarkable and pharmacologically unique property of depressing respiration in the conscious

subject might be a useful tool for the study of the central control of respiration. In 1962, when the writer became interested in the problem of the control of breathing the use of morphine as an investigative tool appeared worth considering. It was soon apparent, however, that the published data on the respiratory effects of morphine were not adequate for the formulation of any hypothesis which might usefully be tested by means of suitably designed experiments. It is true that there was a nearly general consensus that the respiratory centre was depressed by the drug. Despite this consensus, the evidence available left unanswered many important questions, and, even the idea itself has recently been called in question by a leading worker in the field of narcotic pharmacology (Krueger, 1955).

It seemed to the writer that most of the uncertainty, particularly in regard to studies on humans, could be attributed to faulty experimental design. This criticism applies specially to the choice and standardisation of doses used and the paucity of measurements or observations made.

It was decided, in consequence, to design an experiment <u>de novo</u> for the quantitative study of the effects of morphine in man on respiration, oxygen consumption and carbon dioxide output. As a result of encouraging results from some preliminary studies performed during the Summer and Autumn of 1962, the details of the experimental design were decided later that year. The goals of the project were laid down in advance as follows.

1. To measure in detail the effects of morphine on respiration, oxygen consumption, carbon dioxide output and arterial gas tensions in normal subjects and in individuals suffering from left ventricular failure.

2. To determine the relationship of the effects noted to the size of dose administered.

3. To formulate an hypothesis, on the basis of these observations, by which the respiratory depressant and other observed effects of the drug might be explained.

4. To find out whether or not the use of this drug would be likely to increase understanding of the central mechanisms responsible for the control of respiration.

REVIEW OF LITERATURE ON THE PHARMACOLOGY OF MORPHINE

I. HISTORICAL

The preparation of opium from the seed capsules of the poppy plant Papaver somniferum has been practised since prehistoric times and its medicinal use was known to the ancient Egyptian, Persian and Greek physicians. Morphine, which comprises about 10% by weight of powdered opium is a comparatively modern drug. Its isolation, in crude form, was first achieved by Sertürner in 1803 and, during the next two decades, its use in clinical practice appears to have become fairly well known. It was first administered on a large scale by the hypodermic route during the American Civil War when, it is said, many addicts were produced as a result (Maurer and Vogel, 1954). The use of the hypodermic needle was pioneered by Wood around 1853, this worker's wife unfortunately becoming addicted to the drug in this way. The first systematic quantitative studies on the respiratory depressant properties of morphine appear to have been those of v. Bezold (1866), Gscheidlen (1869) and Claud Bernard (1864), according to Krueger (1941). The view that the drug depressed the respiratory centre appears first to have been suggested by Gscheidlen (Krueger, 1941).

The extensive literature on morphine has been very well covered in a number of reviews (Krueger, Eddy and Sumwalt, 1941; Wikler, 1950; Krueger, 1955; Reynolds and Randall, 1957; Eckenhoff and Oech, 1960). The present survey of the literature is more limited in scope than the aforementioned and

has been undertaken also with somewhat different objectives. It will be concerned, mainly, with an analysis of the published data, with particular reference to man, on the effects of the drug on respiration and oxygen consumption. For reasons which will later become apparent, the published reports on possible stimulatory effects of the drug were closely studied. Reports on the circulatory effects of morphine, both in laboratory animals and in man, which appeared to have some relevance to the mechanism of effect of the drug in individuals with left ventricular failure have also been reviewed.

II. THE HYPOTHESIS OF THE 'DUAL ACTION' OF MORPHINE

The view has been advanced that morphine has a dual effect consisting of a mixture of simultaneous stimulation and depression on different parts of the central nervous system (Tatum, Seevers and Collins, 1929; Seevers and Deneau, 1962). The first reference to the diphasic action of morphine, according to Krueger, Eddy and Sumwalt (1941), appears to be in the work of v. Boeck and Bauer (1874), who categorise this action as a phase of stimulation followed by a phase of depression.

The evidence that morphine has stimulant effects is not particularly good. The idea is based mainly on the effect of the drug on the overt behaviour of a few animal species and, also, on the observation that, in many species, very large doses cause convulsions. Evidence that the drug has stimulant effects upon non-addicted humans, is rather meagre, though not entirely lacking.

Signs of increased motor activity after morphine are observed in the mouse, in the domestic cat and probably also in all feline species, and, to some extent, in the dog. In the mouse a curious erection of the tail (Straub reaction) is a fairly constant phenomenon occurring very soon after administration of morphine in suitable dose and associated with circling movements. In the domestic cat motor restlessness associated with signs of sympathetic activity, namely, pilo-erection and pupillary dilatation, very commonly occurs after morphine. This phenomenon appears to be dose related. Tavat and Akçasu (1956) report that doses less than 0.2 - 0.3 mg/kg did not produce motor restlessness in the cat. This dose is at the upper limit of ordinarily used therapeutic doses in man. Doses of this order and greater regularly produced motor restlessness in their cats. Joel and Arndts (1925) stated that doses of 0.1 - 0.2 mg/kg caused definite depression in the cat, while larger doses regularly produced excitement. Doses of 20 mg/kg or larger caused convulsions. Guinard (1890) who used doses of 0.4 - 90 mg/kg reported no obvious narcotic effects. Wikler (1944) reported that morphine 5 mg/kg given to intact cats intravenously initially caused a bradycardia, slowing of respiration and marked sedation, the animal lying quietly on its side and not responding to prodding, pinching or noise. Within 5 - 10 minutes, the pupils dilated widely and the animal became alert and stood up. However, motor activity was poorly co-ordinated, the animal preferring to lie or sit quietly and showed motor restlessness only if disturbed. Larger doses caused spontaneous motor restlessness to appear immediately after administration without any initial period of depression.

Measurement of respiration and oxygen consumption in conscious cats given morphine has only rarely been reported. Such studies have usually shown an increase in minute ventilation and oxygen consumption (Krueger, Eddy and Sumwalt, 1941).

Morphine given to conscious dogs does not cause overt excitement as marked as that reported in cats. However, it has been noted that morphine given to conscious dogs may fail to depress respiration or may even increase this, even in the absence of any signs of overt excitement (Krueger, et al. 1941). This is to be attributed, at least in part, to the role of respiration in this species in promoting heat loss. At an appropriate environmental temperature respiratory depression will occur (Wood and Cerna, 1892; Marshall and Rosenfield, 1937). Nevertheless a period of excitement following administration of morphine has frequently been reported in the dog. Following intravenous doses of 0.5 - 10 mg/kg (Schmidt and Livingstone, 1933) or of 2 mg/kg (Powers, Reid and Gregersen, 1947) a brief period of restlessness and hyperventilation lasting 1 - 2 minutes is regularly seen before longer lasting depression supervenes. Recently, Domer and Josselson (1964) has studied the occurrence of overt excitement in dogs in relation to the dose of intravenous morphine administered. Excitement did not occur after doses less than 0.5 mg/kg. Doses of 0.5 - 10 mg/kg caused the immediate appearance of behaviour which these workers rather inappropriately call "sham rage" consisting of squealing, pawing and snapping lasting 3 - 44 seconds, the duration being roughly parallel with the size of dose. Hyperventilation, tachycardia and salivation appeared some 2-5 minutes later, following which the animal became calm and fell asleep if unmolested.

Large doses of morphine have caused the appearance of convulsions in nearly all laboratory species studied. This has been generally interpreted as evidence of stimulation. An increase in minute ventilation is associated with these convulsant doses. In man, convulsions after morphine poisoning are said to be rare (Krueger et al., 1941).

Documentary evidence that morphine exerts a stimulant effect upon non-addicted humans is unsatisfactory. Statements based on heresay have inferred that in some individuals excitement rather than sedation is produced by the drug (Krueger et al., 1941; Salter and White, 1949). There seems little doubt from the evidence of objective studies that, in clinical doses, the drug exerts a predominantly quieting effect in man (Keats and Beecher, 1952; Keats and Telford, 1960; Smith and Beecher, 1962; Smith, Semke and Beecher, 1962). However, there is very good evidence that morphine sometimes increases ventilation, oxygen consumption and cardiac output in man. Dripps and Comroe (1945) reported that following intravenous administration of morphine subjects often breathed more rapidly and deeply - this they attributed to emotional factors. Starr, Gamble et al. (1937), Dripps and Comroe (1945) and Johnson (1951) report an occasional subject in whom measured minute ventilation rose after administration of morphine. Huggins, Spencer, Geddes, Deavers and Moyer (1957) report a fall in the arterial CO_2 tension initially after 15 mg morphine intravenously, probably indicating a period of hyperpnoea. Drew, Dripps and Comroe (1946) measured the cardiac output in 7 normal individuals during and 40 minutes after intravenous administration of morphine 15 mg. In 6 subjects cardiac output increased during the injection and at 40

minutes a slight increase over the control values persisted in 4 subjects. Prime and Gray (1952) report a mean increase in cardiac output 1 hour after pre-anaesthetic medication, presumably morphine and atrophine, which they attribute, probably incorrectly, to apprehension. Fejfar, Bergmann, Fejfarova and Valach (1957) reported that cardiac output rose significantly in 9 of 20 subjects suffering from mitral stenosis after intravenous morphine. Ventilation had fallen markedly in all but two patients 10 minutes after injection of the drug. Thomas, Malmcrona, Fillmore and Shillingford (1965) gave intravenous morphine in doses of 3 - 10 mg to patients with recent acute myocardial infarction. In 8 of 15 experiments cardiac output increased for part or the whole of the period of observation.

The above review of the evidence indicates that current views of a dual or diphasic action of morphine are not very soundly based on any reliable foundation of experimental evidence. Nevertheless, the observations referred to above that, in some circumstances, morphine produces hyperpnoea, excitement, raised oxygen consumption and increased cardiac output cannot be ignored. Neither can they be explained on the basis of present knowledge.

III. RESPIRATORY EFFECTS OF MORPHINE

The existence of the afore-mentioned effects which have been interpreted by many as stimulatory should not be permitted to obscure the fact that, in the majority of reported studies, morphine has been shown to exert a depressant effect upon respiration. This effect is seen both in laboratory animals and in man.

It seems definite that, under suitable conditions, morphine will depress respiration in man and in all ordinary laboratory species. The cat is, possibly, an exception to this statement to the extent that it is more likely than other laboratory animals to exhibit motor restlessness after morphine. Even so, following the administration to conscious intact cats of doses of morphine that are not too large, probably about 5 mg/kg (Wikler, 1944) respiratory slowing and sedation appear immediately after injection, lasting for some minutes (5 - 10') before overt excitement, with signs of sympathetic discharge, appears. Tavat and Akaçasu (1956) have found that the minimal dose which produces overt excitement and motor restlessness in the cat is 0.2 - 0.3 mg/kg. It would appear crucial to measure the respiratory effects of doses of morphine lower than this, but such experiments have not yet been done. On a weight basis, this range includes amounts commonly used therapeutically in man (14 - 21 mg/70 kg) and not known, except perhaps very rarely to cause excitement in such individuals.

Since anaesthetised and decerebrate cats show respiratory depression after morphine (Dripps and Dumke, 1943; Ngai, 1961) it seems very likely that conscious cats also would so so if suitable doses were administered.

In rabbits, rats, primates and man respiratory depression regularly occurs after administration of morphine, by any route. Dogs, also, suffer respiratory depression after morphine. However, as pointed out in the previous section, these effects may be masked by the influence of a warm environment or by transient excitatory effects similar to those which occur

in cats. Even so, these excitatory effects also become less marked with decreasing dose (Domer and Josselson, 1964).

The pre-war literature on the respiratory effects of morphine reviewed by Krueger et al. (1941) is, subject to the preceding qualifications, consistent with the view that the drug depresses respiration in all laboratory species studied. Later studies, although often reporting the collection of respiratory data only as a subsidiary interest, support this view (Dripps and Dumke, 1943; Hart and McCawley, 1944; Cook, Navis and Fellows, 1954; Miller, Gilfoil and Shideman, 1955; Yim, Keasling Gross and Mitchell, 1955; Ngai, 1961; Rubin, Chernov, Miller and Mannering, 1964; Kokka, Elliott and Way, 1965).

Comparatively few attempts have been made to relate the excitatory or respiratory depressant properties of morphine, in quantitative manner, to the dose used.

As pointed out previously, Wikler (1944), Domer and Josselson (1964) and Tavat and Akçasu (1956) have established a relationship between increasing dose and the liability to cause overt excitement in the cat and dog.

Wright and Barbour (1935) state that, in the rabbit, the minimum dose affecting minute volume of respiration was 0.5 mg/kg. The effect on respiration increased sharply with increasing dose up to 2.0 mg/kg and more gradually from this point to 10 mg/ kg. This would indicate that, over the range used, depression in minute volume increased with the logarithm of the dose administered.

Barlow (1933) also studied the effect of dose on respiratory depression in the rabbit, with similar results. Respiratory depression increased rapidly with increasing dose from the minimum of 0.26 mg/kg to 2.6 mg/kg. Larger doses caused only slightly greater respiratory depression. The minute volume actually increased after the smallest dose though the respiratory rate declined. Earlier work cited by Krueger, Eddy and Sumwalt (1941) also suggested a similar relationship between respiratory depression and the logarithm of the dose.

Barlow (1933) noted a similar relationship between dose and effect in the rat. The range of doses studied was 2.1 - 63 mg/kg. The degree of depression increased rapidly with increasing dose up to 15 mg/kg and thereafter more gradually as the dose was increased further. The depression in respiratory rate following 63 mg/kg was only 3% greater than that caused by 21 mg/kg.

Thus, in the older literature, quantitative data relating respiratory effects to the size of the dose are few, and, are available only for rat and rabbit, the experimental animals which most reliably exhibit respiratory depression after morphine.

Among more recent workers, similar results have been reported. Miller, Gilfoil and Shideman (1955) working with rabbits found that 4 mg/kg produced a 50% reduction in minute volume of respiration. For doses up to 16 mg/kg the respiratory depression was proportional to the dose administered. Doses larger than this were increasingly less effective in depressing respiration Yim, Keasling, Gross and Mitchell (1955), also working with rabbits, found that

mw =

doses above .002 - .004 millimols/kg produced no greater depression than that (to 70% of control value) achieved by the aforementioned dose although the larger doses did cause a longer lasting depression.

Kokka, Elliott and Way (1965) studied the dose/effect relationship in great detail in conscious rats. They found that depression of ventilation increased from 5 mg/kg through 10 - 20 mg/kg when the effect is reversed. The depression caused by 20 mg/kg was in fact slightly less than that noted after 10 mg/kg. This reversal of effect continued as the dose was increased so that the respiratory depression after 40, 80 and 160 mg/kg was not as great as that caused by 10 or 20 mg/kg. The oxygen uptake behaved in a similar fashion.

Unfortunately, data as complete as that published by Kokka et al. (1965) for the rat are not available for human subjects. Huggins, Spencer, Geddes, Deavers and Moyer (1957) administered morphine intravenously to adult surgical patients. The drug was given in increments of 15 mg and 15 - 20 minutes were allowed to elapse before respiratory and other measurements were made. There was a levelling off in minute volume depression at 75 mg and of tidal volume at 30 mg. Doses up to 60 mg produced little change in respiratory frequency. In some respects these results resemble those obtained in the rabbit (Miller et al. 1955) and in the rat (Kokka et al. 1965); but on the whole these findings are difficult to interpret and it seems doubtful whether repeated injections of morphine in the manner described by these workers serve any useful purpose in respiratory studies.

Unfortunately, the majority of modern workers who have studied the effect of morphine on human respiration have not standardised the doses used or were, for other reasons - for example, the use of treatment groups too small for analysis - unable to relate the size of dose to any changes observed (Higgins and Means, 1915; Starr, Gamble, Margolies, Donal, Joseph and Eagle, 1937; Wangeman and Hawk, 1942; Dripps and Comroe, 1945; Johnson, 1951; Eckenhoff, Helrich, Hege and Jones, 1955). The frequent neglect to standardise the doses used is surprising.

It must be emphasised that the respiratory and other effects of morphine demonstrated in animal experiments can seldom be usefully compared with the human studies available. On the basis of body weight the doses used in animal studies have been considerably larger than those used therapeutically or experimentally in the human. This cannot be interpreted as an indication that experimental animals are usually more resistant to the depressant actions of the drug than man. On the contrary, it is to be noted that the depression in ventilation, where such depression occurs, is considerably greater than that seen in human studies, including those to be presented later in the main body of this report. Probably the greater difficulty of measuring pulmonary ventilation in small animals has been responsible for the failure to detect significant changes in ventilation of the order seen after the relatively smaller doses used in man.

Both in human and animal studies, the change in minute ventilation has, in general, been the most reliable index of respiratory depression after morphine.

In the rabbit, the respiratory rate has usually been markedly depressed by the doses used (Cushny, 1913; Macht, 1915; Wright and Barbour, 1935; Hart and McCawley, 1944; Miller, Gilfoil and Shideman, 1955). In this animal, the effects upon tidal volume have been very variable. By contrast, in their study on the rat, Kokka, Elliott and Way (1965) report that the smallest dose used, 5 mg/kg, depressed minute ventilation by reducing the tidal volume, without alteration of the respiratory rate. In human subjects, the changes in respiratory rate and tidal volume have been very variable in all reported studies (Higgins and Means, 1915; Wangeman and Hawk, 1942; Dripps and Comroe, 1945; Lasagna and Beecher, 1954 a, b; Eckenhoff, Helrich, Hege and Jones, 1955; Orkin, Egge and Rovenstine, 1955; Eckenhoff and Oech, 1960), with, more often than not, no change which could be regarded as significant, in respiratory rate or tidal volume. Although the statement that morphine depresses all phases of respiration, namely, minute volume, respiratory frequency and tidal volume,(Goodman and Gillman, 1965), is neither unreasonable nor improbable there is little or no support for this belief in the published studies on man or laboratory animals.

IV. EFFECT ON OXYGEN CONSUMPTION

The data on the effects of morphine upon oxygen consumption in laboratory species are difficult to interpret. The best available study is the report by Kokka, Elliott and Way (1965) on conscious male rats. In this study, measurements of respiration and oxygen consumption were made at 15 minute intervals following drug administration. It was found that 5 mg/kg caused a small

fall in oxygen uptake beginning at 30 minutes after injection and ending at 90 minutes. A more marked decline to 70% of the control value occurred after doses of 10 - 20 mg/kg 60 minutes following injection. Doses larger than 20 mg/kg caused a reversal of effect so that 80 mg/kg had little effect upon oxygen uptake and 160 mg/kg actually increased oxygen uptake after 60 minutes.

The pre-war literature reviewed by Krueger, Eddy and Sumwalt (1941) is rather confusing. The majority of studies on the dog, according to these authors, have shown a decrease of metabolism with doses of less than 20 mg/kg, a decrease which was usually greater than 15%. They believe that the different doses used would explain some of the discrepancies in the literature, though other factors, such as, biological variability, environmental conditions and experimental procedures, seem to be involved. It is worthy of note that Barbour, Gregg and Hunter (1930) found markedly raised basal metabolic rates in 3 dogs after 6 - 10 weeks daily treatment with morphine.

Data in respect to other animal species are rather scanty. Pulewka (1927) reporting 3 experiments in mice found a marked decline in oxygen consumption. Wright and Barbour (1935) reported that oxygen uptake was not significantly altered by morphine in rabbits. However, their published charts indicate that oxygen consumption was slightly greater than the control values throughout the post-drug period in one experiment with 0.5 mg/kg.

Thus, the older studies in laboratory species are not inconsistent with the findings of Kokka, Elliott and Way (1965) that small doses of morphine depress and larger doses, either cause no significant change, or increase oxygen uptake.

By contrast, the majority of experiments on human subjects have demonstrated a fall in oxygen consumption following administration of morphine, though not necessarily a significant one by the investigators' standards. The extent of this decline in oxygen consumption has varied considerably (Higgins and Means, 1915; Boothby and Rowntree, 1924; Schoen, 1924; Bornstein and Holm, 1926; Anderson, 1929; Stark, 1929; Herxheimer and Kost, 1932; David, 1934; Starr, Gamble, Margolies, Donal, Joseph and Eagle, 1937; Wangeman and Hawk, 1942; Johnson, 1951; Keats and Beecher, 1952). In some individual experiments an increase in oxygen uptake was recorded following drug administration, though this increase was usually either considered non-significant or not commented upon (Higgins and Means, 1915; Bornstein and Holm, 1926; Herxheimer and Kost, 1932; Starr et al. 1937; Orkin, Egge and Rovenstine, 1955).

In a majority of the above quoted studies the doses used were not standardised and it is not possible to infer whether the variation in the results reported is to be attributed to dose effects or to other factors. The small numbers of measurements and replications usually reported, also make interpretation difficult. As an illustration of the difficulty of interpreting these results, it may be noted that in the two experiments reported by Bornstein and Holm (1926), the smaller dose - on the basis of body weight - caused a fairly marked fall in oxygen uptake, while the larger dose caused a small increase. In both subjects, ventilation fell markedly, the depression being somewhat greater after the larger dose.

There is little definite information in the literature on the relationship in the human between the dose of drug and the change in oxygen consumption. David (1934) compared two groups of 10 subjects each given 0.14 and 0.22 mg/kg (10 and 15 mg/70 kg) morphine respectively. Four post drug measurements of oxygen consumption were made during each experiment. The depression in metabolic rate was only very slightly greater after the larger dose though the authors do not mention whether they considered this small difference to be significant.

Huggins, Spencer, Geddes, Deavers and Moyer (1957) administered morphine intravenously in successive increments of 15 mg to convalescent surgical patients. Measurements of ventilation and oxygen consumption, among others, were made 15 - 20 minutes subsequent to each injection. The authors state that 90 mg produced very little change in oxygen uptake, although this dose caused a marked depression in minute ventilation and tidal volume. The published charts, however, indicate a slight decline in oxygen uptake which was apparently broken by a slight increase after 45 mg had been administered. Unfortunately, the primary data on which the chart is based were not published. The authors mention that the oxygen uptake per ml of ventilation ("ventilatory equivalent") while little affected by doses up to 30 mg showed a variable though marked increase following the larger cumulative doses. This would be consistent with a virtual increase in metabolism though the authors do not mention this possible interpretation of their results.

The available evidence thus indicates that the depression in oxygen uptake following the administration of morphine to human subjects may, occasionally, be marked. Frequently, however, the fall in oxygen consumption is very slight, or, an actual increase may occur. The significance of the changes reported and the existence or otherwise of any definite relationship to the dose administered cannot be inferred by examination of the published data. On the available evidence, the most that can be said is that after doses such as are ordinarily used in clinical practice, morphine causes, more often than not, a rather variable and usually slight fall in oxygen uptake. However, occasionally an increase in oxygen consumption will occur, even in association with a modest or marked fall in ventilation.

V. EFFECT OF MORPHINE UPON THE VENTILATORY RESPONSE TO CARBON DIOXIDE

It has long been recognised that morphine diminishes the respiratory response to increased concentrations of carbon dioxide in inspired air. Loewy (1890) and Lindhard (1911) were the earliest workers to study this phenomenon in man. The latter author, relating alveolar ventilation to alveolar carbon dioxide tension, found that this curve was markedly displaced by morphine. Later workers have added little to these earlier conclusions. It has been generally agreed that, following administration of morphine, the ventilatory response to increased concentrations of carbon dioxide in inspired air is reduced, whether these concentrations are achieved by adding carbon dioxide in known amounts to

the inspired gases (Prescott, Ranson, Thorp and Wilson, 1949; Keats and Beecher, 1952; Berkowitz, 1961), by increasing the inspiratory dead space Herxheimer and Kost, 1932), or by the use of a rebreathing circuit (Eckenhoff, Helrich, Hege and Jones, 1955).

Similar results have been reported from experiments on laboratory species (Cushny, 1913; Macht, 1915; Wright and Barbour, 1935; Dripps and Dumke, 1943).

Many modern studies in man have used the displacement of the alveolar ventilation/alveolar carbon dioxide response curve as a measure of drug effect, chiefly in relation to the evaluation of the respiratory depressant properties of the newer analgesics and of the effects of the opiate antagonists. Dripps and Comroe (1947), Nielsen and Smith (1952) and Lambertsen, Kough, Cooper, Emmel, Loeschke and Schmidt (1953) have studied, in normal subjects, the relationship between ventilation and the carbon dioxide concentration of the inspired air or alveolar carbon dioxide tension. Loeschke, Sweel, Kough and Lambertsen (1953) first used the displacement of this curve, after administration of narcotics, as a measure of drug effects. In untreated subjects the slope of the respiratory response increases very markedly when concentrations of carbon dioxide in excess of approximately 2% are inhaled, or when the alveolar carbon dioxide tension exceeds about 40 mm.Hg. At that point ventilation increases very sharply with increasing inspired or alveolar carbon dioxide tension. Because of this change of slope, the displacement caused by drugs has been measured in relation to the steepest portion of the curve. Loeschke et al. (1953) using as an arbitrary reference point an alveolar CO_2 tension of 46 mm.Hg report

that 10 mg morphine depressed the ventilatory response to carbon dioxide at that point by approximately 30%. The slope of the response curve was not affected by morphine, in this study.

Seed, Wallenstein, Houde and Bellville (1958) have used the rebreathing method of increasing carbon dioxide concentration in the inspired air, with similar results. The concentration of CO_2 gradually built up to 7 - 8%. These workers, also, measured the displacement caused by morphine at an arbitrarily chosen level of alveolar ventilation on the steeper portion of the response curve. Morphine in doses of 5 and 10 mg caused a displacement to the right, that is, towards higher values of $P_A CO_2$, the displacement being greater after the larger dose. They also report a marked tendency for the magnitude of the drug effect to be proportional to the pre-injection level of alveolar CO_2. In this study, a significant diminution of slope was produced by 10 mg morphine. Both displacement of the curve and change in slope were thought by these authors to indicate respiratory depression. However, it is to be noted that the carbon dioxide output was less depressed by the larger dose, in nearly all subjects - in fact, the excretion of carbon dioxide either did not change or actually increased in 3 subjects. This is not entirely consistent with the claim that both doses depressed respiration, though the authors do not comment on this point.

Other reports from the same laboratory have confirmed this displacement by morphine and related narcotics of the alveolar ventilation/$P_A CO_2$ response curve towards higher values of $P_A CO_2$. (Steinberg, Bellville and Seed, 1957;

Bellville et al. 1960; 1962; Houde et al. 1964; Forrest and Bellville, 1964). A similar displacement of the ventilation/alveolar carbon dioxide tension curve after administration of morphine has been reported by Wilbrand and Matthaes (1958).

An increase in arterial or alveolar PCO_2 following administration of morphine to human subjects breathing room air, in association with a fall in minute ventilation has been recorded by many groups of workers. This situation presumably indicates a decreased sensitivity of the respiratory apparatus to carbon dioxide. An increase in alveolar or arterial carbon dioxide tension, rather exceptionally fails to occur.

Keats and Beecher (1952) report no consistent changes in arterial carbon dioxide tension 1.5 hours after injection of morphine even though ventilation was depressed. Taylor, Scott and Donald (1964) record a non-significant increase in arterial carbon dioxide tension of approximately 1 mm.Hg 30 and 60 minutes after anaesthetic pre-medication. In the former study, arterial puncture was apparently performed at the time of sampling, a procedure which might, as the authors point out, cause overbreathing. In the observations of Taylor, Scott and Donald (1964) - which did not include measurements of ventilation - the premedication contained atropine, which may have inhibited the expected rise (Wangeman and Hawk, 1942).

Other reports available record a rise in alveolar or arterial carbon dioxide tension, usually, though not invariably, a marked one, after administration of morphine to human subjects. In the experiments of Higgins and Means (1915), alveolar carbon dioxide tension rose slightly following administration of

16 mg morphine sub-cutaneously to human subjects in 4 instances. A maximum increase of approximately 2 mm was noted in some individual observations. The rather small mean increase of slightly less than 1 mm.Hg appears to have been significant. The mean fall in total ventilation was of the order of 8%. Loeschke, Sweel, Kough and Lambertsen (1953) reported a significant increase of 2.6 mm.Hg following 10 mg morphine intra-muscularly which was associated with a non-significant fall in ventilation. Berkowitz (1961) reports a mean increase in arterial carbon dioxide tension of 4 mm.Hg after 15 mg morphine in 5 subjects who experienced, at the same time, a 7% decline in ventilation. Eckenhoff, Helrich, Hege and Jones (1955) studied 4 subjects who received 10 or 15 mg morphine intra-muscularly. All showed an increase in alveolar carbon dioxide tension in association with a reduction in minute ventilation. In one of these subjects the ventilatory response to carbon dioxide was increased. Wilbrand and Matthaes (1958) using doses of 20 and 10 mg intravenously, also found that an increase in alveolar carbon dioxide tension usually occurred. Huggins, Spencer, Geddes, Deavers and Moyer (1957), who used cumulative doses of morphine in successive increments of 15 mg, report similarly that, despite the marked fall in ventilation, alveolar and arterial carbon dioxide tensions increased.

The observations of Thomas et al. (1965) indicate that 5 - 10 minutes after intravenous morphine in doses of 3 - 10 mg in 15 experiments the arterial carbon dioxide tension increased 3 - 5 mm.Hg in all but one subject in whom there was a rather marked fall (from 44.5 to 39.0 mm.Hg), presumably due to

overbreathing: among 4 subjects in whom arterial CO_2 tension was measured 20 - 30 minutes after injection, 3 showed an increase and one a decrease as compared with the control value. In this study ventilation was not measured.

The increased arterial or alveolar carbon dioxide tension which usually occurs after morphine may be taken, in the formal sense, as indicative of diminished sensitivity of the respiratory centre to carbon dioxide. However, these changes have not been studied in relation to the other changes caused by morphine, namely, changes in oxygen uptake, carbon dioxide output and minute ventilation achieved by subjects breathing room air.

It has been claimed that the use of ventilation/alveolar carbon dioxide response curves provides a more sensitive index of drug effects than direct measurement of ventilation because significant changes in minute ventilation may not occur despite an increase in alveolar CO_2 tension (Loeschke et al. 1953) or because changes in ventilation may represent both respiratory and metabolic effects (Seed, Wallenstein, Houde and Bellville, 1958). These arguments appear rather unrealistic and it seems very doubtful that the results yielded by the use of these curves justify the claims advanced. The experiments reported appear to have done little more than confirm that morphine and related narcotic drugs depress respiration, a point on which general agreement has already been reached. They have not contributed any fresh data which would support a plausible hypothesis of drug action. One suspects also that valuable information has been lost in these studies, because of the failure to undertake orthodox respiratory measurements. For example,

the interesting observation by Seed et al. (1958) that 10 mg morphine apparently caused a smaller decline in CO_2 output but a greater fall in ventilation than 5 mg is surely worth pursuing.

It may be pointed out, further, that neither these experiments nor any other available observations have proven that morphine influences respiration through a change in the sensitivity of the centre to arterial CO_2 tension. That human beings and laboratory animals become more tolerant of pain and other forms of discomfort including increased levels of carbon dioxide in inspired air after administration of morphine is a well established fact. There is no proof that respiratory depression is occasioned by this diminished sensitivity and consequently no evidence that the diminished ventilatory response to carbon dioxide is an authentic measure of drug induced respiratory depression. By the same token, it is not justifiable to assume that other non-narcotic drugs which may depress or stimulate respiration will necessarily cause a displacement in the response curves measured as above described (v. Keats and Beecher, 1952). Some workers would appear to have subscribed to this fallacy (Steinberg, Bellville and Seed, 1957; Bellville, Escarraga, Wallenstein, Wang, Howland and Houde, 1962). So far as is known the narcotic family are the only group of drugs with this property of attenuating the effects of afferent stimuli of noxious or unpleasant character (and acute hypercapnia and dyspnoea are stimuli of essentially this character), in sub-anaesthetic dose. That this property and that of causing respiratory depression are in some way linked, is a reasonable supposition. That the one property bears some causal relationship to the other is, in present state of knowledge, an entirely unacceptable proposition.

VI. STUDIES AND THEORIES BEARING ON THE MECHANISM OF ACTION OF MORPHINE

According to Krueger et al. (1941), Gscheidlen (1869) was probably the first to suggest that morphine altered respiration by depressing the respiratory centre. The ideas of the earliest workers have been well reviewed by Cushny (1913). These early workers, were aware of the increased carbon dioxide content of the blood, the diminished ventilatory response to increased concentrations of inspired CO_2, and the prolongation of apnoea from forced breathing in morphinised animals. The general consensus appeared to be that the drug depressed respiration by depressing the excitability of the respiratory centre.

Higgins and Means (1915) considered the possibility that a peripheral mechanism was operative when they reported that in 3 of 4 experiments on human subjects physiological dead space decreased after administration of morphine, a change which they interpreted as evidence of broncho-constriction. These workers concluded that morphine could affect respiration both by causing broncho-constriction and by depressing the respiratory centre. Although morphine has long been known to cause broncho-constriction in laboratory species (Shemano and Wendel, 1965) it seems doubtful that this effect is important in man.

Cushny (1913), reporting experiments on rabbits, drew attention to the similarity between the effects of morphine and those of vagotomy in depressing the respiratory rate while leaving the tidal volume unchanged or even increased. He was thus led to investigate the possibility that morphine acted by blocking

the delivery of afferent vagal stimuli to the respiratory centre. It was demonstrated that augmentor vagal impulses were depressed by morphine while inhibitory vagal impulses were facilitated. He concluded, however, that the centre itself rather than the afferent pathway, was depressed by the drug.

Cohen and McGuigan (1924) disputed the proposition that morphine depressed the respiratory centre directly and suggested instead that respiration was depressed because sensory impulses from the periphery which normally stimulated the centre and maintained its tone were blocked.

Maloney and Tatum (1930) working with anaesthetised rabbits also studied the effect of the drug on the respiratory response to afferent nerve stimulation. In the morphinised animal, they found that the respiratory responses to stimulation of the sciatic nerve and of the intact skin were reduced. They found also that the apnoeic response to increased intra-pulmonary pressure was enhanced and the acceleratory response to negative intra-pulmonary pressure depressed. It was concluded that morphine acts as a central respiratory depressant, reducing the responsiveness of the centre to accelera-tory impulses including the stimulus of carbon dioxide and increasing the effectiveness of inhibitory vagal impulses.

Henderson and Rice (1939) working with anaesthetised rabbits reported that all vagal reflexes were made more effective by morphine. Its effect on the respiratory reflexes was such as to cause a slower respiratory rate and frequently to reduce the tidal volume. However, the response to cutaneous nerve stimulation was increased by morphine.

Dripps and Dumke (1943) reported that decerebrate dogs and cats given i.m. morphine, while showing the expected depression in the respiratory response to carbon dioxide stimulation, exhibited an enhanced chemoreceptor sensitivity to stimulation by Na CN. It was felt that this increased sensitivity was apparent rather than real.

Ngai (1961) studied the effect of morphine upon the response to vagal stimulation and to electrical stimulation of the pontile pneumotaxic centre, the medullary inspiratory and expiratory centres in vagotomised mid-collicular decerebrate cats. The effect of morphine in the unstimulated preparation was to cause respiratory slowing of various degrees, the respiratory amplitude as recorded on a kymograph remaining unchanged or, at times, increasing. Repeated doses of 1 - 2 mg/kg were administered. The acceleration induced by stimulation of the pontile pneumotaxic centre was reduced by morphine as was the hyperpnoea which follows stimulation of the medullary expiratory centre. The threshold for eliciting inspiratory spasm following medullary inspiratory centre stimulation was progressively raised with successive doses of morphine. The drug also reduced or abolished the acceleratory response to central vagal stimulation with low frequency currents; and lowered the stimulus threshold for expiratory apnoea induced by high frequency vagal stimulation. It was concluded that the neural mechanism for respiratory rhythmicity was depressed by morphine and that the apparently exaggerated susceptibility to inhibitory vagal reflexes is the result of central depression. The persistence of inspiratory response to pneumotaxic centre stimulation and the observation that respiratory amplitude either increased or remained

unchanged, suggest that the mechanism controlling respiratory rhythm is mainly affected by morphine.

May and Widdicombe (1954) in experiments on anaesthetised cats also demonstrated that morphine greatly enhanced the Hering - Breuer inflation reflex. These workers, however, suggested that this enhancement is secondary to broncho-constriction with consequent increased activity of the pulmonary stretch receptors.

Breckenridge and Hoff (1952) administered morphine intravenously, in repeated doses, to intact and mid-collicular decerebrate dogs. Conscious intact animals, given 10 - 160 mg intravenously, developed a short initial period of polypnoea followed by a regular sighing rhythm associated with a slight reduction in the rate and amplitude of eupnoea. This pattern of breathing is very similar to that produced by decerebration. The results suggested a release of pontine centres facilitating this type of breathing, which are normally held in check by cortical and other suppressor activity. At mid-collicular level morphine reproduces almost exactly the effect of vagotomy, which further intensifies the deep sighing type of respiration of decerebration and causes eupnoea to disappear completely. The authors suggest that morphine operates generally by inhibiting the action of suppressor mechanisms.

By contrast, Egbert and Bendixen (1964) report that morphine in doses of 2.5 or 5.0 mg administered intravenously post-operatively to surgical patients abolished sighing for approximately one hour, appeared to cause the volume of individual breaths to become constant, and did not significantly affect respiratory frequency or tidal volume.

It is generally agreed that morphine depresses the response to certain stimuli, such as increased inspired carbon dioxide and pain which ordinarily increase respiration. The drug also modifies the effects of vagal stimulation so that vagal impulses which ordinarily cause respiratory slowing are facilitated and those which ordinarily cause respiratory slowing are facilitated and those which ordinarily cause acceleration are depressed. There is no evidence that the depression in ventilation following administration of morphine is caused by this attenuation of effect of afferent stimuli. It would be a truism to point out also that morphine does not cause any paresis of motor respiratory function since following appropriate stimulation or, in the human, encouragement, normal or even excessive ventilatory volumes can be attained.

The conclusions of Ngai (1961) that the primary effect of the drug is to depress the neural mechanism for respiratory rhythmicity is seriously to be questioned. This opinion is based mainly on the observation that, in unstimulated animals, the drug caused respiratory slowing without changes in the breath volume. This could well have been related to the comparatively large doses employed in most animal experiments. Human subjects given much smaller doses frequently show no change in respiratory frequency and no obvious disturbance of respiratory rhythm.

The experiments of Ngai (1961) and of Breckenridge and Hoff (1952) make it clear that, in achieving respiratory depression, morphine acts at many sites, including medullary, pontine and more rostral regions. That a similar situation exists in respect to the analgesic effects is suggested by the work of McKenzie and Beechey (1962). The superficial resemblances

between the effects of the drug and those of vagotomy in the rabbit and the cat (Cushny, 1913; Ngai, 1961) or those of decerebration in the dog (Breckenridge and Hoff, 1952), suggests, not that these drug effects have some facile explanation, but, rather, that these must have very complex origins.

The broncho-constrictor effects of morphine would appear not to be a significant cause of respiratory depression in man. It is, possibly, of some marginal importance in some laboratory species (May and Widdicombe, 1954; Shemano and Wendel, 1965), but it cannot play an important role in the respiratory depression seen in such animals following drug administration.

VII. EFFECTS OF MORPHINE IN PATIENTS WITH LEFT VENTRICULAR FAILURE

At this point it is convenient to run aside from the main stream of the present review in order to consider one of the most important clinical applications of morphine.

Morphine has been used by generations of physicians in the treatment of cardiac asthma. By general agreement the drug is of great benefit and can be life saving in this condition (Fraser, 1923; Bedford, 1939; Luisada, 1940; Hamilton, 1955; Vugrincic, 1955; Daly, 1960). Despite occasional statements to this effect (Hayward, 1955) it seems doubtful that other sedative drugs, for example, barbiturates, are similarly effective in the treatment of acute left ventricular failure. Curiously, morphine appears not to be effective in acute pulmonary oedema induced experimentally in laboratory animals by chemical agents such as epinephrine (Kohler and Barbe, 1955).

The clinical consensus in regard to the use of morphine in acute left ventricular failure is, naturally, deserving of respect, even though derived exclusively from an oral tradition based on the bedside observations of experienced physicians in many countries. Nevertheless it is only fair to point out that the use of morphine in cardiac asthma and left ventricular failure has never been rigorously evaluated, that the rationale of its use is uncertain, and that measurement of the effects of the drug on circulatory and respiratory function in patients with left ventricular failure, has only very uncommonly been performed.

None of the circulatory effects known to be produced by this drug in normal humans or experimental animals would explain the favourable clinical effects believed to be experienced by patients with acute left ventricular failure. Acute pulmonary oedema caused by mitral valve disease or left ventricular failure is immediately related to a rise in pulmonary capillary pressure(Hayward, 1955). Morphine alone in many cases of acute left ventricular failure is said to cause clearing of the clinical signs of lung oedema, in addition to relieving the intense dyspnoea (Fraser, 1923). Yet, the drug appears to exert no very definite effect upon the pulmonary circulation which would explain this.

That morphine produced systemic circulatory effects in experimental animals was known to the earliest workers (Schmidt and Livingston, 1933). The effects noted were bradycardia, dilatation of the blood vessels of the skin and mucous membranes and a fall in systemic blood pressure. Schmidt and

Livingston, (1933), state that the first intravenous injection of morphine in a dog or cat regularly causes a primary fall in blood pressure, but, that repeated injections caused, not a continued or progressive fall, but, rather, a steady recovery of pressure. This phenomenon of tachyphylaxis has been shown to occur, also, in the rat (Evans, Nasmyth and Stewart, 1952).

An intravenous injection of morphine, in a dose of 0.5 mg/kg or over, in a conscious dog, induces marked restlessness, hyperpnoea and tachycardia followed, immediately afterwards, by clinical signs of circulatory collapse, lasting for a variable period which depends upon the dose administered. The stage of excitement and collapse is associated with a fall in the arterial blood pressure which gradually recovers, as the clinical signs of collapse regress. The blood pressure recovers completely though the animal remains sedated. Subcutaneous injection has the same effect though larger doses are required (Schmidt and Livingston, 1933). Morphine also reduces the rise in blood pressure produced by asphyxia or carbon dioxide inhalation and, also, the vasomotor response to afferent nerve stimulation. Schmidt and Livingston (1933) believed that the dilator action of morphine was peripheral while bradycardia was due to a central action of the drug.

Huggins, Glass and Bryan (1951) in experiments on anaesthetised dogs also confirmed the marked vasodepressor effects of morphine. After doses of 0.1 - 5.0 mg/kg there was a decrease in peripheral vasomotor resistance, a fall in blood pressure, an increase in cardiac output and an

increase in blood flow to the head. The extent and duration of the fall in blood pressure increased as the dose of drug was increased and, all doses used caused an increase in the cardiac output. Intra-arterial injection into the carotid artery was more effective in producing all these changes. These authors interpret their results as indicating that the depressor effects of morphine are exerted both peripherally and centrally. The experiments of Breckenridge and Hoff (1952) emphasised the very marked vaso-depressor properties of morphine in the dog. They found that doses of morphine which are administered with safety to decerebrate animals caused so marked a fall in the blood pressure of animals subjected to mid-collicular and medullary section, that the respiratory effects were completely overshadowed.

In the anaesthetised cat, morphine administered intravenously, also causes a prolonged fall in blood pressure (Feldberg and Paton, 1951; Evans, Nasmyth and Stewart, 1952). An immediate fall is also seen in the anaesthetised rat but this, however, is transient and lasts 20 - 30 seconds only (Evans, Nasmyth and Stewart, 1952). In spinal and decerebrate cats the vasodepressor effect is of shorter duration than that seen in anaesthetised animals. The possibility that endogenous histamine, which is known to be released by morphine (Feldberg and Paton, 1950; Nasmyth and Stewart, 1950) might be responsible for the circulatory effects of morphine was investigated by Feldberg and Paton (1951) and Evans, Nasmyth and Stewart (1952). Both groups of workers concluded that released histamine did account for some but by no means all of the observed depressor effects. The last named

authors showed, further, that, in the cat, the effect of morphine on the circulation is mediated partly through the vaso-motor centre and partly through the release of histamine peripherally. In the rat, sensory impulses in the vagus nerve were shown to mediate the whole of the response - since the vaso-depressor effect was blocked by bilateral vagotomy but not by atropine.

Kayaalp and Kaymakçalan (1966) measured the circulatory effects of intravenous morphine in vagotomised conscious cats rendered immobile by gallamine triethiodide. The chief effect of the drug was to induce the occurrence of marked irregularity in the blood pressure record which, in some studies, appeared to have a regular rhythm. Blood pressure fell transiently after the larger doses - 5 to 10 mg/kg. In some animals, the hypertensive response to carotid artery occlusion was considerably reduced by morphine. Anaesthetised cats, given gallamine triethiodide and artificially ventilated, showed a precipitous fall in blood pressure following doses in excess of 2 mg/kg. This initial fall was succeeded by a slowly developing sustained fall. These workers made the interesting observation that the initial fall only, appeared in animals treated with nalorphine, and that this could be blocked with the antihistamine mepyramine. The blood pressure disturbances seen in the conscious animals were corrected by nalorphine.

Few studies have been published of the circulatory effects of morphine in normal human subjects.

Starr, Gamble, Margolies, Donal, Joseph and Eagle (1937), using the ethyl iodide method report a small, non-significant mean fall of 1% in cardiac output of seven healthy subjects. Systolic blood pressure measured with a sphygmomanometer also fell very slightly (2.7%). The dose usually administered was 15 mg.

Papper and Bradley (1942), using the ballistocardiographic method, measured cardiac output in six healthy subjects following morphine 10 mg. Cardiac output measured within 1.5 minutes of drug administration rose in three subjects (by 4, 11 and 20%) and fell in 2 (by 9 and 7%) and was unchanged in 1. Later measurements remained elevated in 2 subjects (7 and 20%) and showed a fall ranging between 4 - 8% in the remainder. The peripheral resistance rose in two subjects (17 and 27%) and fell in two (10 and 18%).

Himmelsbach (1944) reported that morphine, in doses larger than 5 mg significantly increased the rate of blood flow in the hands and forearm of addicts, post-addicts and normal control subjects.

Drew, Dripps and Comroe (1946), also using the ballistocardiographic method, measured the cardiac output in 7 healthy subjects during and after the injection of 15 mg morphine intravenously. During the injection, cardiac output increased in 6 subjects and was unchanged in 1. Measurement of cardiac output 40 minutes after injection showed near normal values in all except one subject in whom the initial elevation had persisted. During injection of the drug, the pulse rate usually increased. The blood pressure, measured with the sphygmomanometer, usually did not change. Of 25 subjects submitted to tilting into the 75 degree head up position, after intra-

muscular injection of morphine, 11 (44%), either fainted or showed signs and symptoms indicative of imminent circulatory collapse. These authors concluded that, while the circulatory effects of morphine are unimportant in the normal supine individual, they assume much more significance when the circulation is put under strain. A similar reaction to tilting has been reported by Helrich and Gold (1964).

Johnson (1951) measured the respiratory and circulatory changes in 9 healthy subjects, 7 male and 2 female, before and 20 - 50 minutes after intravenous administration of anaesthetic premedication consisting of 6 - 18 mg morphine combined with scopolamine. Mean respiratory minute volume and oxygen consumption fell 15% and 6% respectively. There was a mean fall of 9% in cardiac output, though two individuals did show a slight increase. The mean systolic and diastolic blood pressures fell by 9 and 7 mm respectively. There was a mean increase in the peripheral resistance of 5%. In one case there was a rise of 6 mm.Hg in the pulmonary mean arterial pressure, but, in the others, this hardly changed. However, there was a significant increase of 21% in the mean value for the pulmonary vascular resistance.

Prime and Gray (1952) measured cardiac output before and 1 hour after premedication - presumably with morphine and atropine - in 15 healthy patients. One hour after premedication mean cardiac output increased from 4.8 $\pm$ 0.9 to 6.7 $\pm$ 1.4 l./min. The authors did not regard this increase

as due to the drugs administered but, rather, to apprehension. Since the oxygen consumption fell, this explanation is possibly inadequate.

It is, unfortunately, not possible to evaluate the contribution made by scopolamine and atropine to the results recorded in the last two studies cited. This contribution could well have been significant, since both drugs stimulate ventilation and scopolamine itself has a slight sedative effect (Wangeman and Hawk, 1942).

Thomas, Malmcrona, Fillmore and Shillingford (1965) measured the circulatory changes in 15 experiments on subjects with recent acute myocardial infarct, before and after 3 - 10 mg morphine administered intra-venously. In 7 instances, there was no change in cardiac output after injection; in 8 studies cardiac output was increased for part or the whole period of observation. In none did a convincing fall occur. Arterial mean blood pressure decreased transiently in 7 patients and in 1 case, there was a persistent fall. One subject showed a very marked and progressive fall in blood pressure following 3 mg which recovered when the legs were elevated. Peripheral resistance did not change in 6 instances and, in 8 studies there was either a consistent or a transient fall. Central venous pressure was unchanged.

The known circulatory effects of morphine may, therefore, be summarised as follows. The immediate effect of the drug, particularly when administered intravenously, is, frequently, to cause a fall in the systemic blood pressure which may be quite sharp. In the cat and in the dog, and, apparently, also in some human studies a sustained fall in the blood pressure may follow this transient depressor phase. During the initial vaso-depressor phase, cardiac

output increases in the dog. In human studies, a transient increase in cardiac output also frequently occurs, and a sustained rise also has been noted in some studies. In many cases, the cardiac output is little changed. The fall in blood pressure is associated with a fall in the systemic vascular resistance and the animal studies referred to previously make it clear that there is both a peripheral and a central cause for this. It seems definite that released endogenous histamine is responsible in part for the initial phase of hypotension. More sustained hypotension, when present, has been reversed or inhibited by nalorphine as, also, have the curious irregularities, at times rhythmic, in the blood pressure tracing reported by Kayaalp and Kaymakçalan (1966) in cats. This reversal by nalorphine presumably indicates the existence of a central vaso-motor effect and other data also are consistent with this supposition.

Only uncommonly have respiratory or circulatory measurements been made before and after administering morphine to patients suffering from left ventricular failure. For obvious reasons, studies performed on patients during acute pulmonary oedema have been rare.

Herxheimer and Kost (1932) measured ventilation and oxygen consumption before and 20 minutes after administration in the course of 10 experiments on patients with cardiac failure, and in 6 normal subjects. Normal subjects received 20 mg and cardiac patients 5 - 20 mg sub-cutaneously. The changes in both groups were very similar. Ventilation fell in all subjects and mean

oxygen consumption declined. A slight increase in oxygen consumption occurred in 2 normal and in 2 cardiac studies. When inspiratory dead space was increased, usually by 1 litre, the carbon dioxide retention occurring after morphine was greater in the cardiac group. The subjective effects in the two groups were somewhat different. In normal subjects, unpleasant sensations predominated, as was also noted by the authors in themselves following self-administration, whereas to the cardiac patients, the effects of the drug were very pleasant. Presumably this was related to relief from the burden of dyspnoea and, objectively, the authors state they appeared to be improved.

Resnik, Friedman and Harrison (1935) measured ventilation and oxygen consumption in two patients suffering from congestive failure due to syphilitic aortic insufficiency. Ventilation and oxygen consumption and cardiac output measured by the three sample acetylene test, fell in each case. The moderately severe dyspnoea present before treatment in each case was relieved. It was noted that very similar changes occurred after venesection and bed rest respectively.

Starr, Gamble, Margolies, Donal, Joseph and Eagle (1937) measured the effect of 15 or 30 mg morphine administered to 8 patients with cardiac disease of various types, all seriously ill, though none in congestive failure. Cardiac output was measured by the ethyl iodide method of Starr and Gamble. Mean oxygen consumption, cardiac output and left ventricular work diminished somewhat more than in the healthy control group studied in the same way.

None of the changes were, however, statistically significant. It is worthy of note that the oxygen consumption, while declining in 5 individuals, rose in 3. The authors draw attention to the greater fall in left ventricular work after morphine in the cardiac than in the non-cardiac group.

Scebat and Lenegre (1949) measured the effect of morphine on right heart pressures in 30 patients, all except one (a well compensated mitral), seriously ill. Ten patients suffered from mitral disease and the majority of the remainder from aortic or hypertensive disease. Morphine 10 mg was given to all patients by intra-auricular or intra-ventricular catheter. Right atrial pressure, measured in 19 patients, showed a marked fall in 14 which appeared after 2 - 3 minutes, and attained a maximum in 5 - 20 minutes: this fall was most often transitory and often followed by recovery to higher than control pressures. It rarely lasted as long as 25 - 70 minutes. However, in 5 individuals a variable increase in right atrial pressure occurred which lasted throughout the period on observation.

Right ventricular/$^{\text{mean}}$pressure was measured in 15 patients, in 9 of whom a fall occurred. This appeared after 2 - 5 minutes, was often transient and followed by recovery, though the fall persisted, at times, for the entire period of observation. In 3 cases a significant increase in right ventricular pressure occurred which persisted for the entire study period of more than an hour.

The authors point out that the fall in right auricular and right ventricular pressure observed in a majority of subjects is a desirable effect.

Nevertheless, this effect is often transitory or hardly apparent and, in an appreciable number of studies - 8 out of 34 - the pressure in the right heart chambers was increased by morphine, an undesirable effect in a cardiac patient. Thus while morphine usually has a favourable haemodynamic effect in cardiac failure, this effect is unreliable, and the drug may, theoretically, be harmful in one quarter of such patients.

Fejfar, Bergmann, Fejfarova and Valach (1957) studied the effects of 10 mg , morphine administered intravenously to 21 patients with mitral stenosis. Ventilation, measured 10 minutes after injection, fell in 19 and increased slightly in 2 patients. Cardiac output, in 20 patients, measured 10 - 15 minutes (direct Fick method) after drug administration, increased significantly (10 - 43%) in 9 patients, decreased in 6 and did not change in 5. Oxygen consumption increased in 3 studies, decreased in 5 and did not change significantly in 12 individuals. The authors do not state how the significance of the observed changes was assessed. The majority of patients showed a consistent rise in pulmonary artery pressure and in only two was there a significant decrease. The authors state, though they do not provide supporting data, that patients with initially low cardiac output showed an increase after administration of the drug, and that those with normal output showed no change or a fall. Changes in total peripheral and pulmonary resistance were inversely related to changes in cardiac output. Right and left ventricular work increased with increasing cardiac output. One patient who developed acute pulmonary

oedema before injection of morphine showed the following changes. The pulmonary mean arterial pressure, which rose markedly when acute pulmonary oedema developed, fell only very slightly after injection of the drug. Following injection of morphine, cardiac output rose sharply (24%), apparently a transient increase, pulmonary resistance fell (31%), pulmonary ventilation fell by 35% and oxygen saturation decreased to 68%.

Finlayson, Luria, Stanfield and Yu (1961) studied the effect of hexamethonium and morphine in 5 patients suffering from mitral or aortic valvular disease who developed pulmonary oedema during cardiac catheterisation. The principal findings during pulmonary oedema included a marked rise in pulmonary artery and pulmonary wedge pressure, low cardiac output, and, in the two instances where this was measured, a rise in systemic arterial pressure. Four patients treated with hexamethonium showed a rapid and dramatic response; the fifth patient treated with intravenous morphine, oxygen and venous tourniquets improved much more slowly.

Other workers have reported similar pressure changes in patients, almost invariably suffering from mitral valve disease, who developed acute pulmonary oedema during cardiac catheterisation. The effect of morphine was not investigated in these studies (Lenegre, Scebat, Besson, Benchemoul and Damien, 1953; Gorlin, Lewis, Haynes, Spiegl and Dexter, 1951).

Roy, Singh, Bhatia and Khanna (1965) measured the effects of morphine on the pulmonary and systemic circulation in 4 male subjects who had recovered from high altitude pulmonary oedema and were asymptomatic at the time of the study. These authors had used morphine to good effect in

patients with high altitude pulmonary oedema who did not respond completely to oxygen therapy. The control pulmonary blood volume was significantly increased in two subjects and within the normal range in the other two. Morphine 10 mg injected into the pulmonary artery, in each case caused the pulmonary blood volume to fall - the mean fall was 26% and the range 15 - 40%. A slight (2 subjects) or a moderate (2 subjects) fall in heart rate, cardiac index and stroke index occurred. Femoral arterial, pulmonary arterial and left ventricular filling pressures fell slightly, but these changes were not significant. The systemic vascular resistance increased somewhat, while the pulmonary vascular resistance was not altered. The authors appear to consider that the decrease in pulmonary blood volume, the fall in cardiac output and the reduction in ventricular filling pressures are related to the beneficial effects of the drug in pulmonary oedema.

Sharp, Bunnell, Griffith and Greene (1961) considered the possibility that morphine might favourably influence the physical properties of lung tissue since these are known to be altered in pulmonary congestion and acute pulmonary oedema. They found that 10 mg morphine given intravenously to 3 patients with acute pulmonary oedema due to arteriosclerotic, rheumatic valvular or hypertensive heart disease exerted no significant effect on lung compliance or pulmonary resistances.

The aforementioned reports do not explain completely how morphine might benefit patients suffering from acute left ventricular failure. There is general agreement that the drug, both in healthy subjects, and in those suffering from cardiac failure, causes ventilation to fall. Dyspnoea, when present, is

relieved. In a majority of experiments morphine has caused oxygen consumption to decline, though not necessarily to any marked degree. A few subjects, however, both normals and those in congestive failure, experience an increase, at times a marked increase, in oxygen consumption. Whether or not morphine can reverse the circulatory changes in acute pulmonary oedema has not been settled by the rare observations recorded on the effects of the drug in this disorder. The results of such studies have not been consistent, and, as the great majority have been performed on patients suffering from mitral valve disease, the findings may not necessarily apply to patients with pulmonary oedema due to other varieties of heart disease. It is evident that more complete respiratory and circulatory studies, both in normal subjects and in patients with congestive cardiac failure, are needed before a satisfactory evaluation of the effects of the drug in left heart failure can be made.

Even on the basis of these rather limited observations, it is useful to consider how the respiratory, metabolic and circulatory effects reviewed earlier might be relevant to the benefits derived by individuals suffering from left ventricular failure. The hypotensive effects noted in animal experiments have not been prominent in human studies, but do occur, very rarely in marked degree. Peripheral dilator effects, however, are the rule and, if hypotension is not severe, would presumably contribute to drainage of the lung by relieving the load on the left ventricle, with consequent relief of symptoms. The effectiveness of ganglion blocking agents in relieving dyspnoea and in reducing elevated systemic venous and right heart pressures in patients with congestive

cardiac failure and acute pulmonary oedema suggests that these peripheral dilator effects of morphine may be of equal value (Sarnoff, Goodale and Sarnoff, 1952; Kelley, Freis and Higgins, 1953; Ellestad and Olson, 1956), Yu et al. (1958). Not infrequently the cardiac output rises, at times considerably, and, no doubt, this is one cause of the absence of significant hypotensive effects in most recumbent human subjects given morphine. An increase in the cardiac output, even a transient one, might also contribute to relief of the pulmonary congestion. Nevertheless, a marked rise may well be tolerated poorly by some individuals with coronary artery insufficiency or myocardial infarction. These arguments are largely speculative since, a rise in cardiac output does not invariably, nor even perhaps in the majority of cases, occur. When such an increase has been recorded in patients with heart failure, a fall in the right heart or pulmonary artery pressure has not necessarily followed.

The fall in ventilation which nearly always occurs after therapeutic doses of morphine may well, in itself, be of benefit to patients in severe left ventricular failure. There can be no question of the subjective benefits to the patient occasioned by the relief of dyspnoea. Does this improvement involve more than the relief from the severe discomfort of dyspnoea analogous to the role of the drug in relieving pain, or, does cardio-pulmonary function improve measurably after morphine? While the literature can supply no certain answer to this question, it would be helpful to set out certain considerations which seem to have some bearing on the matter.

Patients with heart disease have reduced vital capacity and pulmonary compliance and patients with pulmonary oedema, in addition, show increased resistances - both inspiratory and expiratory - to air flow (Brown, Fry and Ebert, 1954; Sharp, Griffith, Bunnell and Greene, 1958). For these reasons among others, the oxygen cost of increased ventilation and the work of breathing are higher than normal in patients with congestive cardiac failure (Hoeschen, Gold, Cuddy and Cherniack, 1962; Cherniack, Cuddy and Armstrong, 1957). Further, many reports indicate that when high levels of ventilation are achieved actively or passively in normal subjects, changes in ventilation are responsible for the major portion of changes in oxygen uptake: and that as the upper limit of ventilation is approached the oxygen cost rises very rapidly with little increase in ventilation (Cournand, Richards, Bader, Bader and Fishman, 1954; McKerrow, and Otis, 1956; Murray, 1959). Presumably this would be true also of patients with severe cardiac failure and acute pulmonary oedema with marked tachypnoea.

Also there is some evidence from the work of Yamamoto and McIver (1960) in rats that a sustained very high level of pulmonary ventilation may, in itself, be a cause of pulmonary oedema and cardiac failure even though it may be doubted that levels of ventilation comparable to those induced by these workers occur in clinical practice.

It is possible, therefore, that the reduction in ventilation itself which results from the administration of morphine might achieve a useful saving in energy expenditure with little, if any, increase in hypoxia. It is not known

whether this in fact occurs since the blood gas changes in patients with cardiac failure given morphine have not been studied. It is known, however, that oxygen uptake does not necessarily decline after morphine despite the marked fall in ventilation which usually occurs, and may even increase. When oxygen uptake declines, the change is not necessarily a marked one, and, in fact, it is seldom that the fall in oxygen uptake is of the same order as the decline in ventilation. Some correspondence would, of course, be expected, if the relationship between these two parameters at resting ventilation is as close as that observed during voluntary or passive hyperventilation. These considerations apply both to normal subjects and to patients with congestive cardiac failure. There is in the literature no answer to this conundrum.

The changes in blood gas tensions in patients with congestive cardiac failure following administration of morphine have not been fully studied. Presumably, as in normal subjects, hypercapnia and hypoxaemia will occur. Since many patients with severe left ventricular failure and pulmonary engorgement have a low or low normal arterial carbon dioxide tension, such hypercapnia may not be in every case an important consideration. Thus whether morphine-induced depression in ventilation and its accompaniments, hypercapnia and hypoxaemia, are physiologically useful, whether they represent an acceptable compromise or whether they are in some instances harmful, cannot be inferred from published evidence.

Finally, some inevitable uncertainty enters into a discussion of the benefits of morphine in left heart failure because the effects of the drug in

such patients have never been fully evaluated. Although formal evaluation is not likely to disprove the central tenets of traditional teaching, it is certainly important to find out whether the different categories of heart disease which cause acute pulmonary oedema respond in differing manner to the drug. It would be desirable also to determe the dose / effect relationships and thus improve precision and discrimination in the routine use of morphine.

VIII. OTHER PHARMACOLOGICAL EFFECTS OF MORPHINE

Morphine produces certain other effects, in addition to those on respiration and circulation, which are of less direct importance to the present investigation. These effects will be briefly mentioned only as it is impracticable fully to review the literature on these points.

IX. HISTAMINE RELEASE

Morphine is a potent liberator of endogenous histamine (Feldberg and Paton, 1950; Nasmyth and Stewart, 1950). This has been discussed, in a previous section of this report, as one, though not the sole, factor in the vasodepressor effects of morphine. Such released endogenous histamine is, no doubt, also responsible for some of the clinically less important effects of morphine, namely, local wheal formation, conjunctival and palpebral erythema, pruritus, abdominal cramps, and, possibly also the broncho-constriction observed in some laboratory species.

X. HYPERGLYCAEMIA

Morphine causes hyperglycaemia in man and in all laboratory species studied. Tolerance to this effect develops with repeated administration. It is worthy of note that hyperglycaemia has occurred irrespective of whether or not overt excitement or depression or respiratory stimulation or depression develops following drug administration. The cause of this hyperglycaemia is not completely understood. The available evidence suggests that hyperglycaemia results primarily from an action on the hypothalamic autonomic centres with consequent release of epinephrine from the adrenal medulla. The reaction is diminished by adrenalectomy and adrenergic blockade.

The literature on morphine hyperglycaemia has been reviewed by Reynolds and Randall (1957).

XI. EFFECTS ON ADRENAL GLANDS AND ON HYPOTHALAMUS

After administration to cats, morphine causes the appearance of increased quantities of pressor substances in adrenal venous blood, an indication of adrenal medullary stimulation (Evans, Nasmyth and Stewart, 1952). In the rat, the ascorbic acid content of the adrenal glands diminishes after morphine, evidence that adrenal cortical activity has been stimulated, presumably through release of ACTH. The ACTH releasing effect appears to be mediated partly through release of histamine and partly through adrenalin released from the adrenal medulla, but there is an important residual effect due to unidentified factors, possibly related to a central effect of the drug on

the hypothalamus (Nasmyth, 1954). These observations no doubt partly explain the old observation that morphine is considerably more toxic to adrenalectomised than to intact rats (Lewis, 1923).

Morphine also appears to influence other hypothalamic functions. It markedly inhibits water diuresis and the evidence indicates that this is achieved by an effect upon the hypothalamo-hypophyseal system (de Bodo, 1944).

Summary of Respiratory and Circulatory Effects by Morphine

The literature on the effects of morphine, with particular reference to man, on behaviour, respiration, oxygen consumption and circulation has been reviewed. The literature on the effects of the drug on patients suffering from left ventricular failure has also been reviewed.

In laboratory species and in man the drug is primarily a central nervous system depressant. In some animals, namely, the cat, mouse and dog, morphine, in certain circumstances, causes restlessness, an effect which appears to be related to the dose. In most laboratory species, very large doses cause convulsions, an effect interpreted by many workers as evidence of stimulation. The evidence that morphine ever overtly stimulates or causes excitement in non-addicted human subjects is not good and, mainly, heresay. Nevertheless, there is good evidence that, in certain circumstances, morphine produces hyperpnoea and increases oxygen uptake and cardiac output, both in human subjects and in laboratory animals.

In human subjects and in all laboratory species morphine causes respiratory depression, even though in some species, namely the cat and the dog such depression may not, under all conditions, be apparent. In the rabbit and in the rat - species for which data are most complete - the depression in minute ventilation is proportional to the logarithm of the dose used. The relationship between dose and effect is not known in the human. The doses reported in experiments on laboratory animals are, on a weight basis, considerably larger than those ordinarily used therapeutically in man. Both in human and in animal studies, the change in minute ventilation has been the most reliable index of respiratory depression after morphine. Changes in respiratory rate and tidal volume have been very variable, particularly in man.

The effects of morphine upon oxygen consumption are not definitely known. Experiments with laboratory species have suggested that small doses depress and larger doses either cause no significant change or may increase oxygen uptake. In the majority of studies in man, oxygen consumption was depressed by morphine but what relationship these changes bear to the dose administered cannot be inferred from the published data. In some studies, the drug apparently caused oxygen uptake to increase even though ventilation fell.

Morphine diminishes the respiratory response to increased concentrations of carbon dioxide in inspired air. The drug also causes an increase in alveolar or arterial carbon dioxide tension in association with a fall in ventilation. The displacement of the ventilation/alveolar carbon dioxide response curve towards higher values of $P_A CO_2$ has been used by many workers as a measure of drug

effects. The use of such curves has been criticised in the review. There seems to be no good reason for thinking that the drug depresses respiration because of this diminished sensitivity to carbon dioxide.

Morphine also attenuates the effects upon ventilation of other varieties of afferent stimulation. The increased respiration normally seen after painful stimulation is diminished and afferent vagal impulses are altered so that inhibitory impulses are enhanced and acceleratory reflexes inhibited or depressed.

Because of these effects upon nociceptive and other afferent stimulation some workers have suggested that respiration is depressed because of interference with afferent impulses while others have postulated that it is the responsiveness of the centre itself, rather than the strength of afferent stimulation which is depressed. The peripheral effect of the drug as a bronchoconstrictor has occasionally been assigned some importance in the respiratory depressant properties of the drug. It is doubtful that this last named effect of morphine is an important cause of respiratory depression in man. Studies on decerebrate and brain stem preparations suggest, by contrast, that the drug acts at many sites, including medullary, pontine and more rostral regions.

Morphine produces systemic circulatory effects in laboratory animals and in man. The drug causes a fall in the systemic blood pressure, peripheral vasodilatation and, frequently, a rise in cardiac output. The fall in blood pressure may be transient, but, in the cat and in the dog, is often prolonged.

In human subjects, the vaso-depressor effects have not been marked though occasional subjects have shown a steep and prolonged fall in systemic blood pressure. However, circulatory studies on man using modern techniques have been few.

Circulatory and respiratory measurements in patients suffering from heart failure after administration of morphine have, only uncommonly, been reported. In the majority of such studies, ventilation and oxygen uptake fell. In some studies, however, oxygen uptake rose. The circulatory changes reported have been very variable. Many patients suffering from left heart failure have shown an increase in pulmonary artery or right atrial pressure, and others, a decrease after administration of morphine. An increase in cardiac output has been reported, in one report, to have occurred in several subjects. One group of workers report a decrease in pulmonary blood volume, in cardiac index and in left ventricular filling pressure following administration of morphine to patients convalescing from high altitude pulmonary oedema. The literature on the circulatory and respiratory changes after administration of morphine to individuals suffering from left heart failure is not extensive. Also, the majority of patients reported in the post-war studies have suffered from mitral valve disease.

The mechanism whereby morphine might cause clinical improvement in patients suffering from left ventricular failure has been discussed. It is possible that the peripheral vaso-dilator effects of morphine - like those of ganglion blocking agents - and, the increase in cardiac output, when this occurs, might each contribute to relief of pulmonary congestion. It is possible that

the fall in ventilation which regularly occurs after administration of morphine might itself be of benefit to patients in left ventricular failure. It is not known whether this decrease in the greater than normal work of breathing would be achieved without an undesirable increase in the degree of hypoxia.

EXPERIMENTAL DESIGN, METHODS, MATERIALS AND STATISTICAL TREATMENT OF RESULTS

Experimental Design

After some preliminary studies, which will not be reported in the present Thesis, the following experimental design was laid down.

Treatment Groups

Three categories of subjects were studied :-

1. Fit subjects not suffering from pulmonary disease or cardiac failure treated with morphine ("normal subjects"). These subjects were divided into four treatment groups to whom doses of 5, 10, 15 and 20 mg/70 kg body weight morphine respectively were administered. These treatment groups contained respectively 6, 9, 9 and 4 subjects.

2. Moderate to severely ill patients suffering from left ventricular failure at the time of the study. These subjects were complaining of exertional dyspnoea, were orthopnoeic and exhibited clinical evidences of pulmonary congestion. To this group, morphine 15 mg/70 kg was administered. There were 6 subjects in this group.

3. A group of 4 fit subjects not suffering from pulmonary disease or heart failure ("normal subjects") treated with soluble phenobarbitone in doses of 3.14 - 3.64 mg/kg.

The normal subjects were in-patients at the time of study and volunteered on request. The purpose of the experiment and the procedures to be adopted were fully explained to them. Each subject was studied once only. The patients in left ventricular failure were invited to co-operate in studying the effects of a drug which, it was explained, would in any case be used in treatment. There was no definite plan of allocation of subjects except that no normal subject was ever selected as being suitable for the administration of any particular dose. The majority of studies in the 10 and 15 mg/70 kg groups were performed earlier in the series than those in the other two groups. It was intended, at the start, that the treatment groups should contain equal numbers of subjects, but, in the event, this proved not to be practicable because of the great pressure on the facilities of the laboratory. It would have been helpful if the 20 mg/70 kg group were larger. However, the small size of this group has proved, in practice, to be not a serious inconvenience. The numbers in the other treatment groups, though unequal, are entirely satisfactory for statistical treatment.

Experimental Procedures

A standard experimental procedure was laid down in advance and closely adhered to in each subject. All experiments were performed in one of two rooms in the Department of Medicine, Royal Infirmary. Entry into this room by other persons was not permitted after commencement of recording.

All experiments were performed in the forenoon. Subjects were permitted a light breakfast at the same time as other patients in the ward

at about 7 a.m. and reported to the laboratory between 9 - 9.15 a.m. After weighing, normal subjects lay supine with one pillow on a comfortable trolley covered with a soft mattress of Dunlopillo for 30 - 40 minutes before any procedures were attempted. After this period of rest, a brief outline of the procedures to be used was given. Patients suffering from left ventricular failure were studied sitting up in their beds supported by a back rest. They were wheeled from the ward to the laboratory on the morning of the experiment. Otherwise the procedure for studying these patients was identical with that described for normal subjects.

Venous and, when required, arterial catheters were then inserted under strict asepsis. A 12 inch polythene catheter, of outside diameter 1.34 mm, was introduced percutaneously (Berneus, Carlsten, Holmgren and Seldinger, 1954) into an antecubital vein, usually the left. The catheter was tested for free reflux, filled with heparinised normal saline and protected with a light plastic two-way tap. In two subjects, in whom venous catheterisation proved unsatisfactory, a Gordh needle was inserted into a vein on the dorsum of the left hand.

In 13 normal subjects treated with morphine, in 3 patients in the group with left ventricular failure, and in 3 subjects in the group treated with soluble phenobarbitone, a similar catheter was inserted into the Brachial artery of the same side using an identical technique. Thus arterial gas tensions could be measured only in approximately one half of the normal

subjects treated with morphine. These facilities were not available for many of the earlier studies and, when this service became more regularly available, arterial puncture occasionally failed.

After insertion of the venous and arterial catheters, subjects breathing room air were made to expire into a Tissot spirometer by way of a low resistance valve whose measured dead space was 60 mls. A light nose clip prevented leakage through the nostrils. During the ensuing practice period of not less than 20 minutes, the spirometer bell was washed out with expired air four or five times. During this period, the subjects became familiar with the circuit and none showed evidence of discomfort or complained of difficulty with breathing into the valve.

Experimental Protocol

All experiments were performed according to an identical protocol which, for convenience, has been outlined on the attached diagram (figure 1). Each study is, in effect, divided into consecutive four minute recording periods, during which ventilation was continuously recorded on the spirometer drum. These recording periods are separated by intervals of one minute, during which a sample of expired air is removed from the spirometer which is then emptied. Arterial blood samples, when taken, were withdrawn at the start of the second minute of each recording period.

Five control periods, extending over a total of 24 minutes, and 12 post drug periods, extending over 60 minutes, were recorded. In occasional

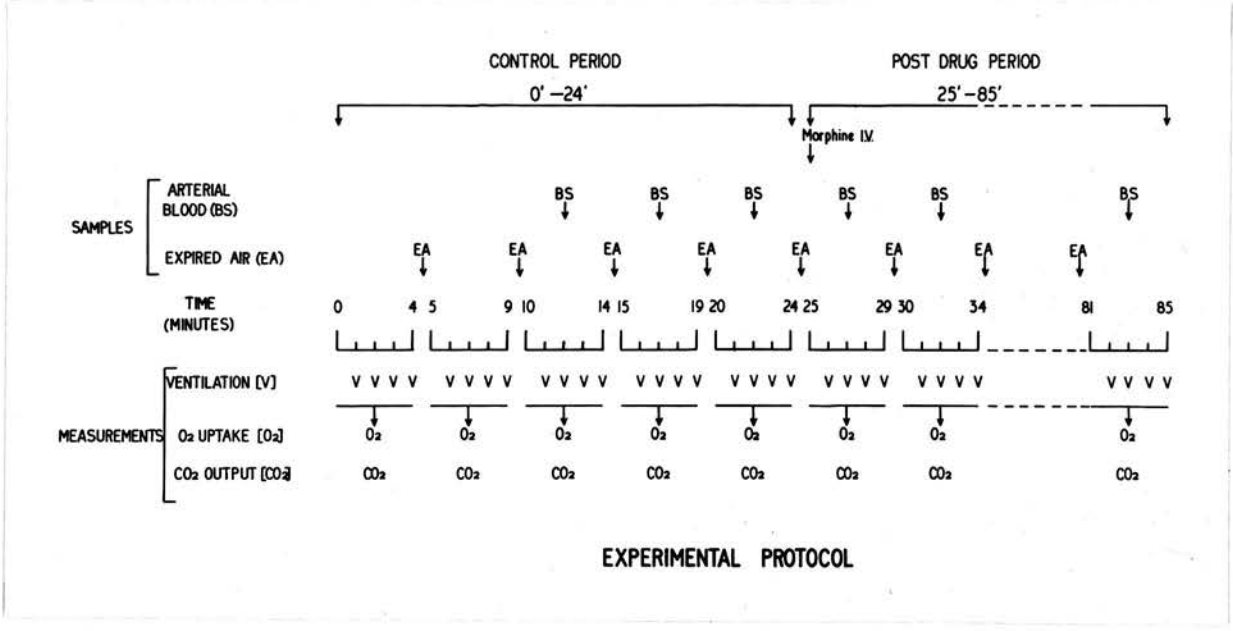

Figure 1.

DIAGRAM OF EXPERIMENTAL PROTOCOL

studies, 1 - 3 minutes were lost during the post drug period because of delays in emptying the spirometer or in replacing the recording paper. These minor departures from the protocol are, for the present purposes, of no importance.

Blood samples were withdrawn during the last 3 control periods. Because of the pressure on the laboratory facilities, sampling was not always performed during the entire post drug period.

The experimental protocol, in consequence, yielded the following data :-

1. Minute by minute records of ventilation, respiratory frequency and tidal volume over a continuous period of approximately 85 minutes, except for the regular interruptions noted previously.

2. Mean measurements derived from the recorded minute ventilation and the analysis of expired air, of oxygen uptake and carbon dioxide excretion per minute over the same period. Occasional samples of expired air were lost.

3. In 13 cases, arterial blood gas tensions at intervals of 5 minutes, consisting of 3 control and 9 - 12 post drug samples.

Morphine sulphate, in the dose selected, was made up to a volume of 10 ml with sterile saline before recordings were started. The drug was administered as a single rapid injection through the venous catheter, exactly at the commencement of the first period immediately following the last control period. Soluble phenobarbitone was made up and administered in exactly the same manner.

Throughout the experiment, the apparent state of alertness of the subject was recorded as frequently as appeared to be necessary throughout the period of the study.

Laboratory Techniques

Spirometry

One of the two Tissot spirometers was used during each study. The calibration factors were respectively 1.016 and 1.416 litre/cm, the respective volumes being 80 and 105 litres. They were calibrated by the standard method of filling the bell of the instrument with a measured quantity of air displaced by a known volume of water. The smaller instrument was calibrated by myself and cross-checked against that of the larger instrument, which had, some time previously, been calibrated. Close agreement was found between the two calibrations.

Minute by minute measurements of ventilation and respiratory frequency were made. The volume displacement of the spirometer was measured from the inscribed record to the nearest 0.1 cm by means of an engine divided rule. The number of breaths during each minute were enumerated direct from the tracing. The mean volume per breath (tidal volume) was calculated from the measured volume related to the number of completed breaths enumerated in that minute.

Where arterial carbon dioxide tensions were available, alveolar ventilation was calculated, in the usual manner, by subtracting Dead Space

from Total Ventilation. Physiological Dead Space was calculated in the standard manner by the use of the equation :-

$$V_{D_{CO_2}} = \frac{P_aCO_2 - P_ECO_2}{P_aCO_2} \cdot V_E$$

Oxygen uptake and carbon dioxide output were calculated from the measured volume of ventilation and the results of the analysis of the expired air samples. For calculation of the oxygen uptake in subjects breathing room air, the standard formula was used, namely :-

$$\dot{V}_{O_2} = \dot{V}_E \left(\frac{F_{I_{O_2}} \times F_{E_{N_2}}}{F_{I_{N_2}}} - F_{E_{O_2}} \right)$$

Samples of expired air were taken into paraffin lined syringes of 50 ml capacity. Gas analysis was performed by myself on the same day on a Haldane gas analysis apparatus as modified by Lloyd (1958). The results of duplicate analyses, which were done on all specimens, agreed within 1% or less. The reliability of the paraffin lined syringes used in this laboratory has been personally evaluated. It has been found that, provided these syringes are kept well greased, they hold the contained gases extremely well over a period of 48 hours at least and probably longer. For each experiment, a set of duplicate specimens was analysed at the end of the day's run and significant differences from the initial result were rarely found.

Arterial blood samples were taken into heparinised syringes which were immediately capped and handed over for analysis. Arterial carbon dioxide tensions were measured by means of the Severinghaus electrode (Severinghaus, 1959), oxygen tensions by means of the Clark cell (Bishop and Pincock, 1959) and pH by means of an E.I.L. glass electrode system.

In accordance with standard practice (Fed Proc 1950) measurements were expressed, unless otherwise stated, in the following units:-

Ventilation ($\dot{V}$)	L/min/sq.m. BSA, BTPS
Respiratory frequency (f)	Breaths/min.
Tidal Volume (volume per breath)	L. BTPS
Oxygen uptake ($\dot{V}_{O_2}$)	L/min/sq.m. BSA, STPD
CO_2 output ($\dot{V}_{ECO_2}$)	L/min/sq.m. BSA, STPD

Body surface area was read off from a nomogram calculated from the subjects' height and weight according to DuBois and DuBois (1915).

Statistical Analysis of Data

A standard method of statistical treatment was employed.

For each subject, in respect to each function measured, the control and post drug means were compared, in the usual manner, by the use of Student's "t" test. The level of significance chosen was 0.05. Where highly significant differences between variances were present, the procedure recommended by Bailey (1959) has been used for testing the statistical significance of differences between means.

In each treatment group the individual changes were treated as normally distributed variables, and the significance of the difference from zero of the mean change observed was tested by the use of the standard formula :-

$$t = \frac{\bar{x}}{s\sqrt{n}}$$

Differences among the treatment groups were tested, in the first instance, by analysis of variance, before more detailed testing using Student's "t" values was used. Where justified, the relationship of observed changes to dose administered has been studied by the calculation of appropriate regression slopes. The significance of the slopes was tested in the usual way by the use of the attached estimate of its standard error.

The control data relating to the normal subjects in the four treatment groups have been tested for homogeneity as to age, minute ventilation and oxygen uptake by analysis of variance.

Since oxygen uptake, carbon dioxide output and arterial carbon dioxide tensions are each linked to ventilation, the changes in these measurements have been further explored by the methods of regression analysis. By the use of these methods, it is possible to find out, provided that suitable regressions can be calculated, whether changes in these parameters have occurred independent of changes in ventilation. The method used has been as follows. In each treatment group a common regression slope has been estimated separately for control and post drug periods by the method of covariance analysis (Snedecor, 1962). In calculating the common control

regressions, all 5 available control periods have been used. The common regression lines so estimated have then been compared in respect to slope and elevation. Differences in elevation have been tested by calculating the adjusted means and testing for significant differences between these.

In the use of regression analysis in the present study, the most difficult problem has been the presence, in some treatment groups, of evidences of significant slope differences among the individual subjects. Where such differences exist, a common estimate of slope derived in the manner indicated may not be valid. There can be no stereotyped method for dealing with this difficulty and the following measures have been employed, as indicated later. It is sometimes possible to locate the source of heterogeneity, for example, an individual subject or a set of observations which can be removed from the calculations if the experimental protocol will permit this, and, if removal does not distort the observations or introduce bias into their interpretation. At times, a common slope is acceptable as the best available estimate, even though there is evidence of heterogeneity, if there are good grounds for assuming that the slope differences are not marked, especially if there is evidence from other data, that the derived slope must be very close to the true value. Occasionally, however, it has had to be accepted that, owing to heterogeneity of slope,avalid estimate of common regression could not be derived.

Finally, for the purpose of evaluating the significance of differences between the control and post drug means, a decision had to be made on the length of the control period to which the post drug changes should be related.

Although 5 control periods, representing observations over 24 minutes, were available it was decided to refer the changes following drug administration to the final 3 control periods only. This decision, which was taken before the analyses were undertaken, may be justified as follows. It seems reasonable to suppose - and experience supports this - that such changes must be related most genuinely to the period immediately preceding drug administration. Consequently, the use of 5 control periods for these comparisons could well result in the loss of valuable information. The three periods chosen provide 12 individual measurements of ventilation, respiratory frequency and tidal volume, a convenient number for statistical comparison with the more extended post drug period comprising 48 individual observations. Logically, the use of the last control period only should provide a convenient basis for the measurement of changes. This argument has substance, but the procedure is, notwithstanding a less satisfactory one because a valuable measure of statistical control would thereby be sacrificed. Particularly, sources of error and variation which cannot be eliminated from any experiment would be less well allowed for in the statistical analysis if only 4 individual observations were available.

Unfortunately, the control period so selected, yields only 3 individual observations of oxygen uptake, carbon dioxide output and gas tensions. Happily, this has been less of an inconvenience than might be thought, mainly because of the very stable metabolic state achieved in the majority of subjects.

Note on Equipment used in this Project

The sources of the apparatus used in the present study are given below.

The venous and arterial catheters used were "Portrex" catheters supplied by Portland Plastics Ltd., Hythe, Kent.

The Tissot spirometers were manufactured and supplied by:-

Siebe Gorman Ltd.,
Neptune Works, Davis Road, (105 litre instrument)
Chessington, Surrey.

G. Plant and Son Ltd.,
Bull Street, Harborne, (80 litre instrument)
Birmingham, 17.

The Severinghaus pCO_2 electrode was manufactured by National Welding EquipmentCo., 219 Fremont Street, San Francisco, California.

The Clark electrode was made in the Engineering Workshop, Department of Medicine, Queen Elizabeth Hospital, Birmingham.

The E.I.L. replaceable capillary glass electrode system was supplied by Electronic Instruments Ltd., Richmond, Surrey.

The respiratory valve used was the low resistance instrument described by Theron, Zwi and McGregor (1958).

RESULTS IN NORMAL SUBJECTS TREATED WITH MORPHINE

Personal Particulars and Control Observations

The personal particulars relating to all subjects studied are given in Table 1. The control measurements for minute ventilation, oxygen consumption and carbon dioxide excretion are set out in Table 2.

The control data relating to the normal subjects in the four groups treated with morphine, have been tested for homogeneity by analysis of variance. There is evidence of significant heterogeneity among the treatment groups in respect to age ($.025 > P > .02$) and detailed testing shows that this is due to the 15 mg/70 kg group in which the mean age is greatest.

The control minute ventilation also shows some slight evidence of heterogeneity among the treatment groups ($P = .05$, nearly) and further tests show that the control minute ventilation in the 20 mg/70 kg group is significantly greater than that of the 5 mg/70 kg group. The other two groups show no significant differences between themselves and are neither significantly different from the 5 or 20 mg/70 kg group.

In respect to oxygen uptake and carbon dioxide output, the normal treatment groups show no evidence of significant heterogeneity.

Variability, expressed as the ratio of the estimated standard deviation to the mean (S.D./mean), in respect to control minute ventilation and oxygen uptake has also been tested for homogeneity. The variability in control

oxygen consumption is remarkably small and there are only small and non-significant differences among the four treatment groups in this respect. Variability in minute ventilation is rather greater but the differences between the treatment groups are far from significant (Table 2).

To summarise, the main source of heterogeneity among the four groups of normal subjects treated with morphine, is the age distribution, and, this is due to the rather greater mean age in the 15 mg/70 kg group. There is just detectable heterogeneity in respect to the control minute ventilation attributable to a significant difference between the 5 mg and 20 mg/70 kg groups. There is no evidence of significant heterogeneity in respect to oxygen consumption and carbon dioxide output or variability in ventilation and oxygen consumption. The mean value for oxygen consumption is very close to published figures for adults in the basal state (Boothby, Berkson and Dunn, 1936; Baldwin, Cournand and Richards, 1948).

The possible influence of age on the respiratory effects of morphine will be considered later. The control values show that in every other respect these four treatment groups are very suitable for comparative study of possible drug effects.

Presentation of Data

The results have been assembled and summarised in tabular form and, also, in the form of diagrams which indicate graphically the most important changes attributable to the drug. The present section of the report will deal with the effects of morphine in normal subjects but, as far as

possible, the results relating to other categories of subjects will be presented in the same manner.

In respect to the normal subjects treated with morphine the following tables are presented :-

Measurements of respiration, oxygen uptake, and carbon dioxide output, for each subject during successive 4 minute control and post drug periods (Tables 3, 4, 5, 6)

Mean control and post drug values of the same for each subject in each treatment group with estimates of statistical parameters attached. (Tables 7, 8, 9, 10)

Mean fractional changes in respect to each variable in each treatment group with estimates of statistical parameters (Table 11)

Mean values are presented with the estimate of standard error (S.E.) and standard deviation (S.D.) indicated thus :- $\text{Mean} \pm \underset{(\text{S.D.})}{\text{S.E.}}$
Estimates of slope are presented in the text and in the tables with the standard error attached.

The units employed are those indicated previously, except that in these tables, the carbon dioxide output is expressed as actual output (litres/min STPD) and not related to body surface area.

The level of significance of the observed changes is indicated in the tables by asterisks as follows :-

*	significant	at	or	beyond	.05	level
**	"	"	"	"	.02	"
***	"	"	"	"	.01	"
****	"	"	"	"	.001	"

The diagrams illustrate these changes and will be referred to in the appropriate portions of the text. In addition, the movements of respiration, oxygen uptake and carbon dioxide output have been plotted in relation to time on diagrams (figures 2, 9, 11, 12, 20). In constructing these diagrams the mean values at each period of the experimental protocol have been computed from the individual measurements together with an estimate of the standard error[1]. The latter is indicated in relation to each plotted point on the diagrams. Thus changes in ventilation, respiratory frequency, tidal volume, oxygen uptake and carbon dioxide output could be referred to the time of drug administration.

(1) One subject (R.M.) in the 10 mg/70 kg group has been excluded from these calculations. In this study, continuous measurements of ventilation etc. were made using two spirometers connected in series.

Effect on Respiration of Morphine (5, 10, 15 and 20 mg/70 kg) in normal subjects

Minute Ventilation

Minute ventilation is significantly depressed by each dose administered (Table 11, Figures 2, 3). After 5 or 10 mg/70 kg the mean ventilation increases before depression supervenes (Figure 2). Following administration of 15 or 20 mg/70 kg, an initial increase is not apparent in the pooled observations. However, some individuals in the former group do experience such an increase (figure 7).

Over the entire post drug period of 60 minutes, the fall in minute ventilation in the 5 mg/70 kg group is just short of the .05 level of significance ($1 > P > .05$). After exclusion from the calculations of the initial period during which an increase in minute ventilation occurs, this post drug depression is statistically significant ($.02 > P > .01$). The depression in minute ventilation, measured over the 60 minute post drug period in the 10, 15 and 20 mg/70 kg groups is highly significant.

Analysis of variance shows a significant dose effect in respect to the depression in minute ventilation ($P < .001$). Comparison between the individual treatment groups show no significant difference between the effects of 15 and 20 mg/70 kg ($P > .7$), and significant differences between the 5 and 10 mg/70 kg ($.05 > P > .02$) and between the 10 and 15 mg/70 kg ($.01 > P > .001$) groups. The mean depression in ventilation after 20 mg/70 kg is actually slightly smaller than that caused by 15 mg/70 kg and this may mean that a levelling off of effect occurs after doses in excess of 15 mg/70 kg. A larger 20 mg/70 kg treatment group would have been helpful

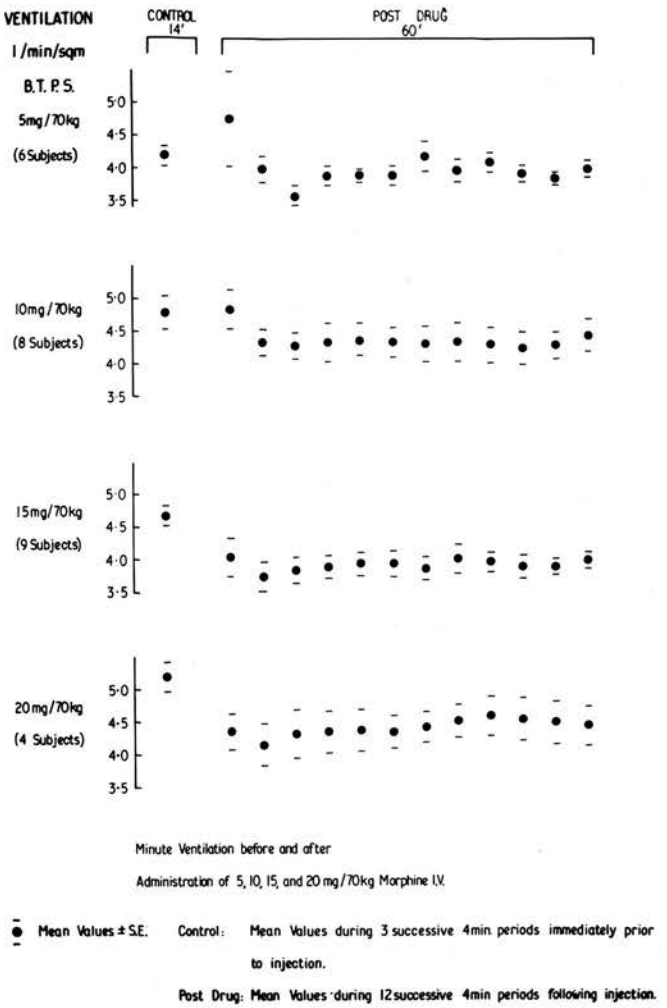

Figure 2

Changes in Respiratory Minute Volume (pooled observations) in relation to time, after 5, 10, 15 and 20 mg/Kg. morphine administered to normal subjects. Each plotted point is the mean value for all subjects ± S.E. (One subject - R.M. - excluded from the 10 mg/70 Kg. group for reasons given in text).

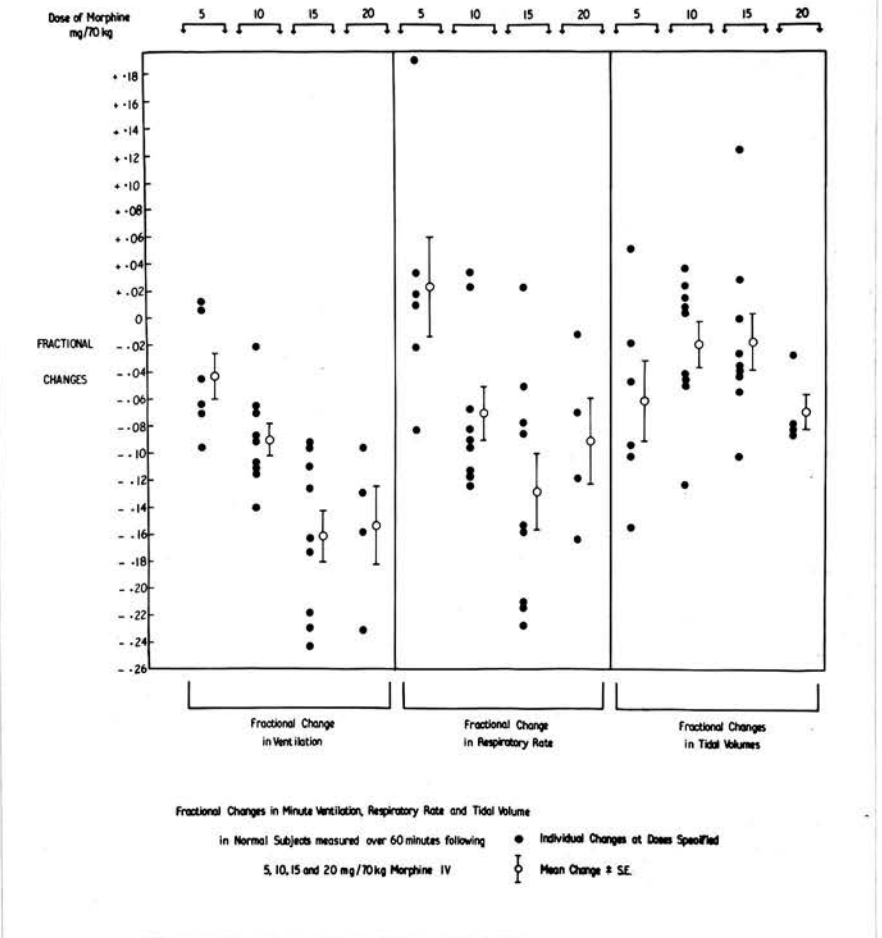

Figure 3

Fractional changes in minute ventilation, respiratory frequency and tidal volume after 5, 10, 15 and 20 mg/70 Kg. morphine in normal subjects. Individual values and mean values ± S.E. for each group are shown. Measurements are over the 60 minute post-drug period.

in deciding this question.

The depression in ventilation is linearly related to the size of dose administered (figure 4). The slope of the straight line which gives the best fit to the observations is highly significant ($P < .001$). The fitted regression has the equation :-

$$\text{Fractional depression in ventilation} = .0050 + (.0089 \pm .0019)^{(1)} \times \text{Dose (mg/70 kg)}$$

Because, as previously discussed, experiments with laboratory species have indicated a logarithmic relationship to the size of dose, the best fitting line to express this has, as a matter of interest, been fitted (figure 3). It will be clear from inspection, that this line is not a good fit to the observations.

These results indicate that, for doses between 5 and 15 mg/70 kg, the depression in minute ventilation, as measured in the present experiment, is proportional to the size of the dose. The results indicate that this linear relationship may break down for doses larger than 15 mg/70 kg. However, because of the rather small size of the 20 mg/70 kg group, and the significantly higher mean age of the subjects in the 15 mg/70 kg group, this question must remain open.

(1) Regression equations will be presented throughout in the form $y = a + (b \pm S.E.) \times X$, where S.E. is the standard error of the estimated slope.

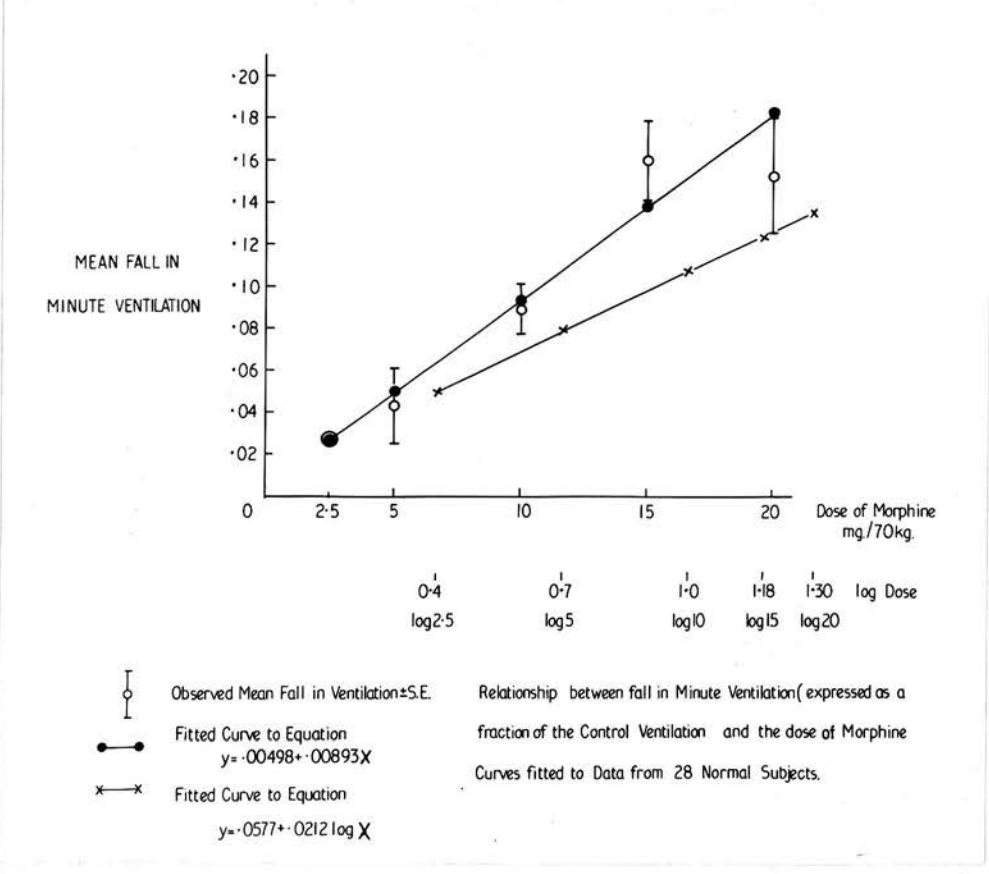

Figure 4

Fitted regression line (least squares method) relating fall in minute ventilation to dose of drug:-

Fractional change

$$V_E = .0050 + (.0089 \pm .0019) \times \text{Dose (mg/70 Kg.)}$$

The fitted line has been extrapolated to include the 2.5 mg/70 Kg. point.

The changes in ventilation observed in the individual subjects are consistent with the group changes noted above (Tables 7 - 10). Each individual in the groups given 10, 15 and 20 mg/70 kg experienced a fall in minute ventilation which was nearly always statistically significant. In 2 subjects, however, both in the 10 mg/70 kg group, this depression was not significant. In the 5 mg/70 kg group, two subjects showed a slight increase in minute ventilation - in both subjects the tidal volume fell significantly. The other 4 subjects in this group all experienced a fall in minute ventilation; in two subjects this was significant, and, in the other two was just short of the .05 level of significance.

The results indicate that all doses of morphine used have a definite depressant effect upon minute ventilation which is proportional to the dose with an apparent levelling off of effect after doses greater than 15 mg/70 kg. In a few subjects, particularly among those given the smaller doses, the depression in ventilation will be slight, or may even not occur.

Hyperpnoea after Morphine

It has been our experience that morphine frequently causes an immediate increase in minute ventilation before depression supervenes (figures 2, 5,-8). Inspection of the data shows that this increase is most frequently present in the treatment groups given 5 and 10 mg/70 kg, is less common in the 15 mg/70 kg group and has occurred in none of the subjects treated with 20 mg/70 kg.

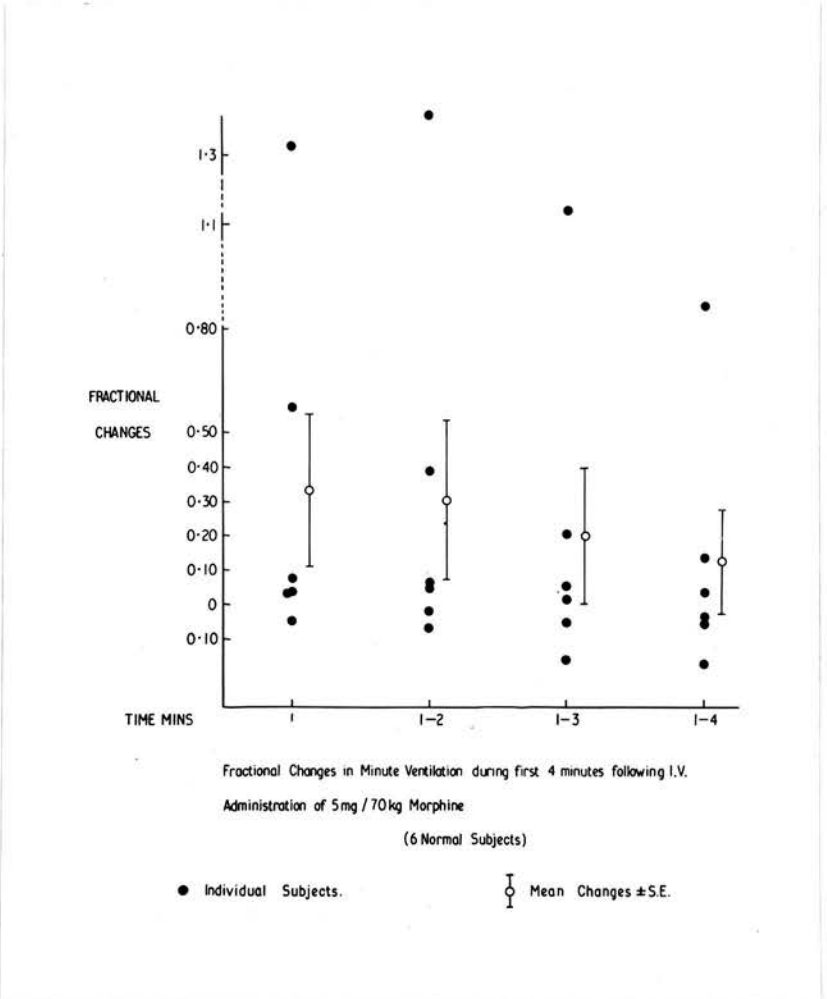

Figure 5

Fractional changes in ventilation at 1 - 4 minutes after administration of 5 mg/70 Kg. morphine (normal subjects). Individual values and mean value ± S.E. shown for each treatment group.

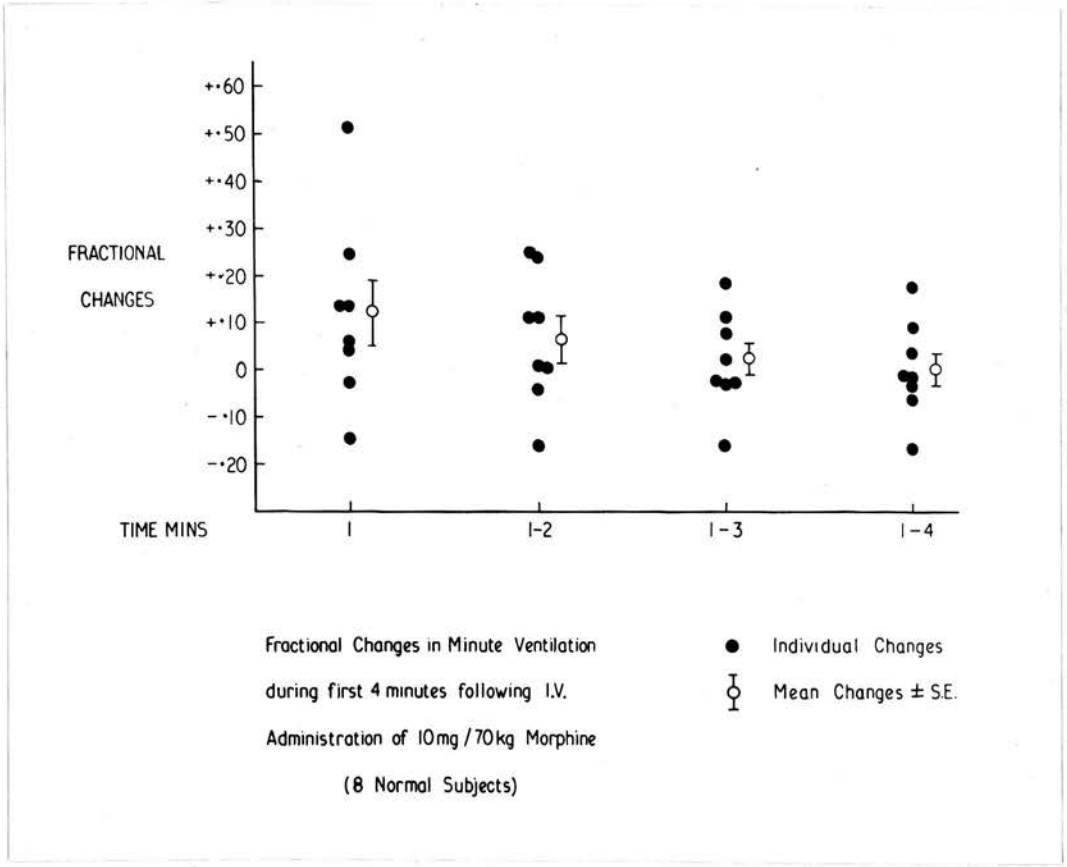

Figure 6

Fractional changes in ventilation at 1 - 4 minutes after administration of 10 mg/70 Kg. morphine (normal subjects). Individual values and mean value ± S.E. shown for each treatment group.

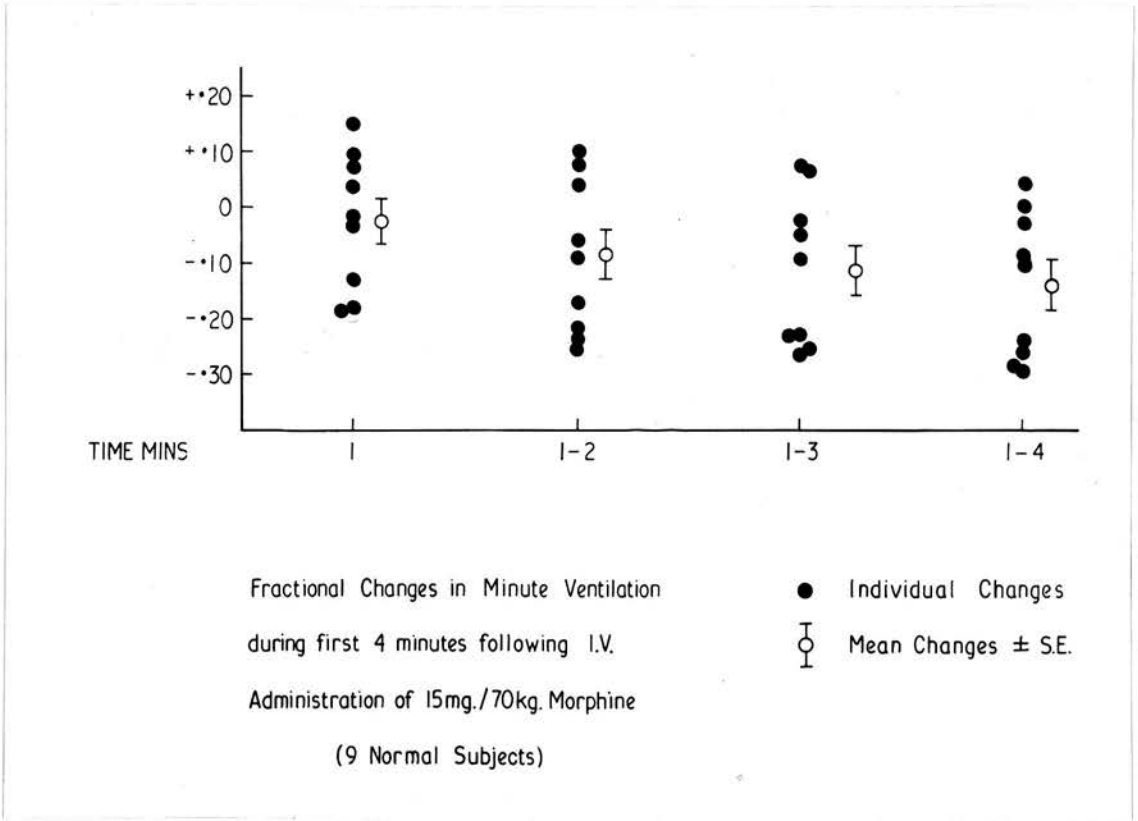

Figure 7

Fractional changes in ventilation at 1 - 4 minutes after administration of 15 mg/70 Kg. morphine (normal subjects). Individual values and mean value ± S.E. shown for each treatment group.

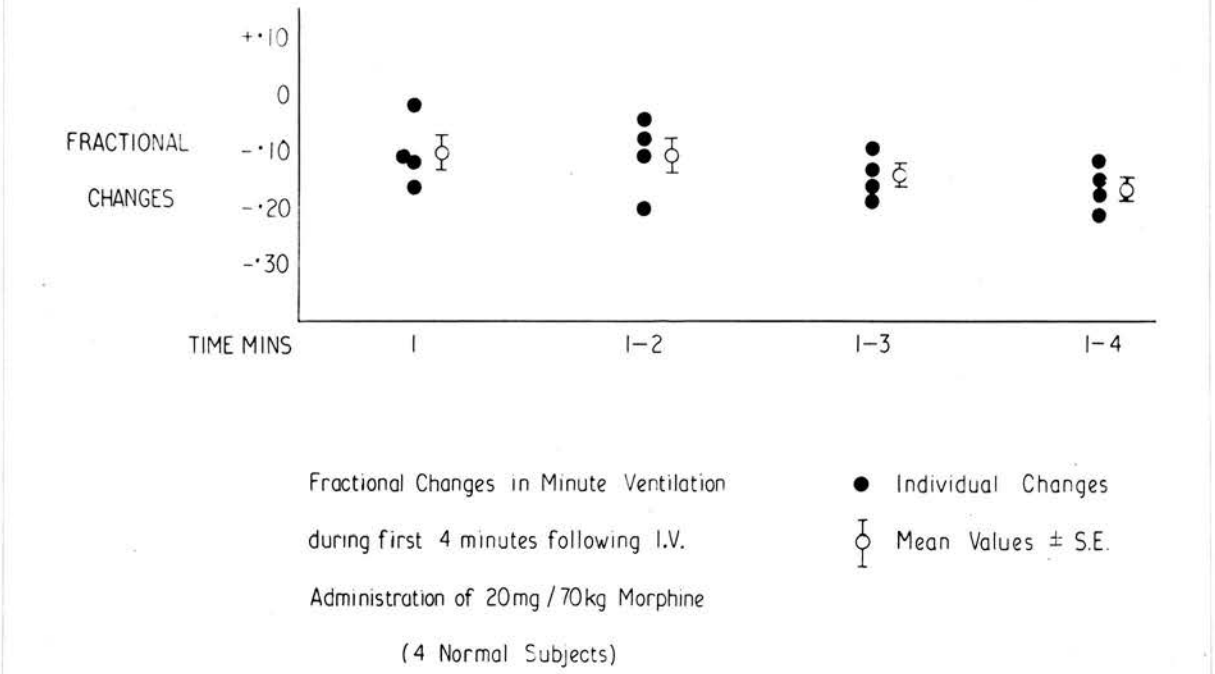

Figure 8

Fractional changes in ventilation at 1 - 4 minutes after administration of 20 mg/70 Kg. morphine (normal subjects). Individual values and mean value ± S.E. shown for each treatment group.

This phenomenon has been analysed in the following manner. The change in ventilation (with the appropriate sign attached) shown by each subject has been calculated at each of the initial four minutes following drug administration. These changes have been treated in the usual manner as normally distributed variables, and the significance of the difference from zero of the mean change so computed has been tested by the use of the standard formula :-

$$t = \frac{\bar{x}}{s\sqrt{n}}$$

A two tailed test has been considered appropriate in this case even though in the 5 and 10 mg/70 kg groups, there is only slight evidence that the drug causes any immediate depression of ventilation.

The changes so calculated are set out in Table 12 and illustrated in the diagrams (figures 5,-8). Inspection of the plotted values indicates that after 5 and 10 mg/70 kg, a large increase in ventilation was not uncommon during the first minute following drug administration and, further, that an immediate fall in ventilation was distinctly uncommon in these treatment groups. This initial overbreathing, where present, regresses very quickly and has largely disappeared by the third minute. In the 15 mg/70 kg group, ventilation increased during the first minute in 4 subjects, and fell in 5 subjects. None of the 4 subjects given 20 mg/70 kg experienced an initial increase in ventilation. The depression in ventilation at the first minute after injection, even in this small group of 4 subjects, is significant ($.05 > P > .02$).

Thus, in all the treatment groups, there is a gradual decline in ventilation during the first four minutes after injection, either from initially high levels (as in the 5 and 10 mg/70 kg groups) or following an immediate decline (figures 5,-8).

Although the majority of subjects given 5 or 10 mg/70 kg morphine experience an initial increase in ventilation - in some cases a very large increase - in neither group is the rather large mean increase statistically significant ($P > .3$ and $>.1$ respectively). Since there is no significant difference between these two treatment groups in this respect, the data have been pooled, but, even after pooling, the mean increase of 21% is still short of the .05 level of significance ($P = .05$, nearly). This failure, to attain an acceptable level of statistical significance, is no doubt to be attributed to the rather large variance.

Subjects treated with 15 mg/70 kg less commonly show an initial increase in ventilation, though increases of 9 and 15% occurred in two subjects. There was a mean fall in ventilation at the first minute in this group of approximately 2%, a non-significant change. As previously noted, subjects in the 20 mg/70 kg group experienced an immediate and significant depression in ventilation, the mean change being approximately 10%.

This change in ventilation (with appropriate sign attached) at the first minute after injection is linearly related to the dose administered (figure 10). The slope of the regression line fitted to the observations by

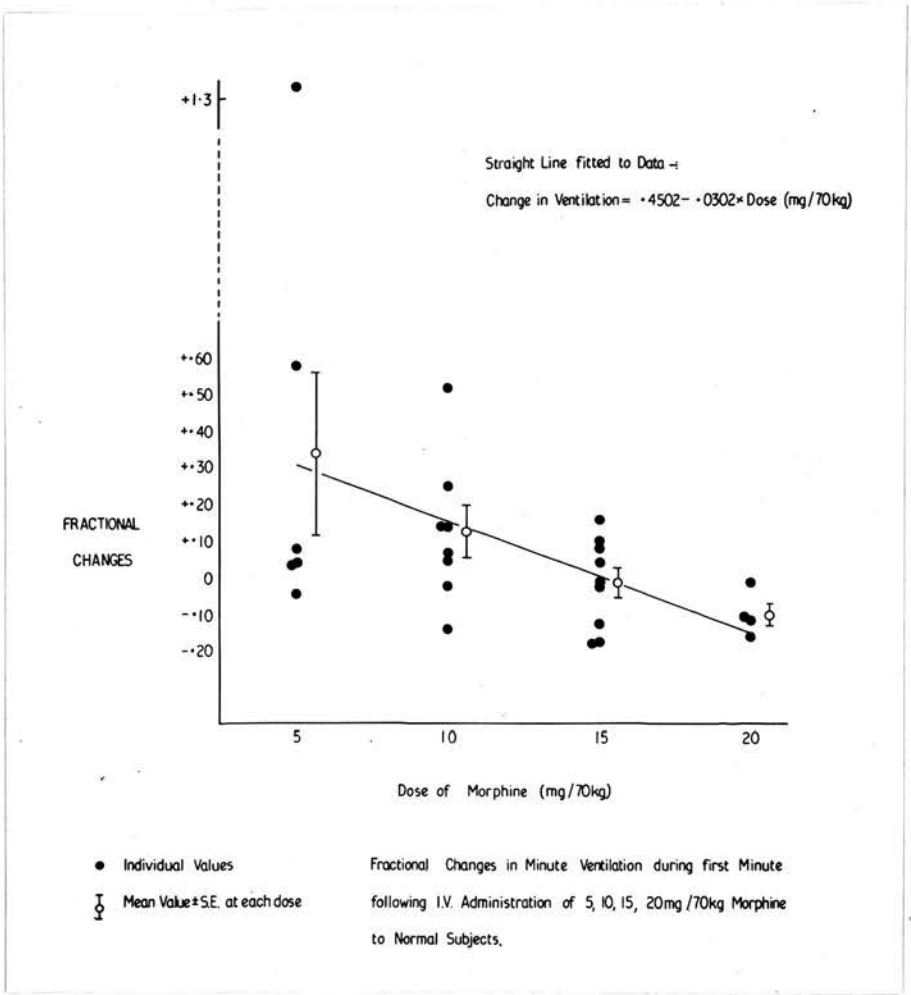

Figure 10

Fitted regression line (least squares method) - changes in ventilation at 1 minute post-drug related to dose of morphine (normal subjects).

Fractional change

$$\dot{V}_E = .4502 - (.0302 \pm .0106) + \text{dose (mg/70 Kg.)}$$

the method of least squares is significant ($.01 > P > .001$). The fitted regression has the equation :-

$$\text{Fractional change in ventilation} = .4502 - (.0302 \pm .0106) \times \text{Dose (mg/70 kg)}$$

Because of the marked variability of these initial changes after administration of morphine an attempt was made to locate some of the factors which might contribute to post drug hyperpnoea. This initial change in ventilation does not correlate with the levels of control ventilation ($r = .093$, $n = 14$), or with the level of oxygen uptake ($r = -.033$, $n = 14$). There is a suggestion that this post drug increase might be related to the variability of the control ventilation as measured by the individual standard deviations ($r = .312$, $n = 14$ $P > .1$). A larger number of observations would be needed to decide this point.

It may, however, be taken as established that morphine frequently causes, in man, an initial increase in ventilation lasting 1 - 2 minutes at most before sustained depression supervenes. This, presumably, may occur after any dose, although no subject in the 20 mg/70 kg group showed such an increase in ventilation. This tendency shows a highly significant inverse relationship to the size of the dose so that the initial increase is most marked after 5 mg/70 kg and decreases steadily thereafter. It cannot, therefore, be doubted that this hyperpnoea is an authentic drug effect. Nevertheless, the great variability, quantitatively, in this response, suggests that the phenomenon is influenced by factors, other than the dose of drug itself,

which are unpredictable in appearance and, consequently, not yet amenable to control. The possible relationship to the variability of the control ventilation suggests that these factors might relate to the internal environment - physiological or psychological.

Effect of Age on Respiratory Depressant Effects of Morphine

It is desirable to consider whether the fall in ventilation after administration of morphine is dependent upon the age of the subject. It has been pointed out in a previous section of this report that the treatment groups show evidence of significant heterogeneity in respect to age which was attributable to the high mean age of the 15 mg/70 kg group. This relationship has been studied in the following manner.

The regression slopes relating change in ventilation (expressed as a fraction of the control value) to age of subject have been calculated for each treatment group, and, these slopes have been compared in the usual manner by covariance analysis (Table 13). The estimate of slope is significantly different from zero only in the 15 mg/70 kg group ($.01 > P > .001$). This slope is negative, apparently indicating in this group a tendency for the older subjects to experience a greater depression in minute ventilation after morphine. The slope estimates in the other treatment groups are not significantly different from zero.

Covariance analysis brings out significant slope differences among the treatment groups ($.05 > P > .025$) and further analysis shows that this is

due to the 15 mg/70 kg slope. If despite the presence of significant slope differences, the sums of squares are pooled, the common slope estimate so derived is far from significant. The estimate of common slope derived, following exclusion of the 15 mg/70 kg group, is also, not significantly different from zero, and is, numerically rather close to the former. It seems likely, therefore, that the significant negative slope and the high correlation between age and respiratory depression, in the 15 mg/70 kg group are spurious. The failure to demonstrate a relationship between changes in ventilation and age in the other treatment groups and the loss of significance when the sums of squares are pooled make this conclusion almost certain. The alternative explanation that this relationship holds only with doses of 15 mg/70 kg is rather improbable.

Consequently, it seems likely either that the relationship between age and depression of minute ventilation is a purely chance finding or, that some other factor which is correlated with age is present in the 15 mg/70 kg group, in greater degree than in other groups. The clinical histories were therefore scrutinised in an attempt to locate such a factor (Table 1). These show that the 10 and 15 mg/70 kg groups contain an excess of subjects with hypertension or cardiovascular disease. In the 10 mg/70 kg group, there were no symptoms referable to vascular disease except in one subject who had recovered from a recent myocardial infarct. In the 15 mg/70 kg group, 2 subjects had recent myocardial infarcts and 2 had recent transient cerebrovascular accidents. All subjects were, of course, fit and free from symptoms at the time of study. It seems difficult to understand how the response to morphine might have been influenced by the above factors.

It appears advisable therefore to investigate more fully the possible influence of age and clinical status on the respiratory depressant properties of morphine. Meanwhile, it would be wise, for the present, to keep an open mind on the matter.

Effect on Respiratory Frequency (figures 3, 9 tables 7 - 11)

The changes in respiratory frequency in relation to time are illustrated in figure 9. The pooled values show a slight initial increase in respiratory frequency after 5 or 10 mg/70 kg and an immediate decline after 15 or 20 mg/70 kg. Sustained depression thereafter is apparent in the 10, 15 and 20 mg/70 kg groups. The net effect in the 5 mg/70 kg group would appear to be slight.

The mean changes, as measured over the 60 minute post drug period, are significant in the 10 and 15 mg/70 kg groups ($.01 > P > .001$) and not quite significant ($.1 > P > .05$) in the 20 mg/70 kg group, probably because of the small size of the last named. In the 5 mg/70 kg group, there is a slight and non-significant mean increase ($P > .5$). One subject only in this last-named group showed a significant depression in respiratory rate. In another, there was a significant increase and in the remainder, the changes were not significant. A majority of subjects who were given 10, 15 or 20 mg/70 kg experienced a significant decline in respiratory frequency. Only 2 subjects in the 10 mg/70 kg group and 1 each in the 15 and 20 mg/70 kg groups failed to show a significant change (Tables 7 - 10, 11. Figure 3).

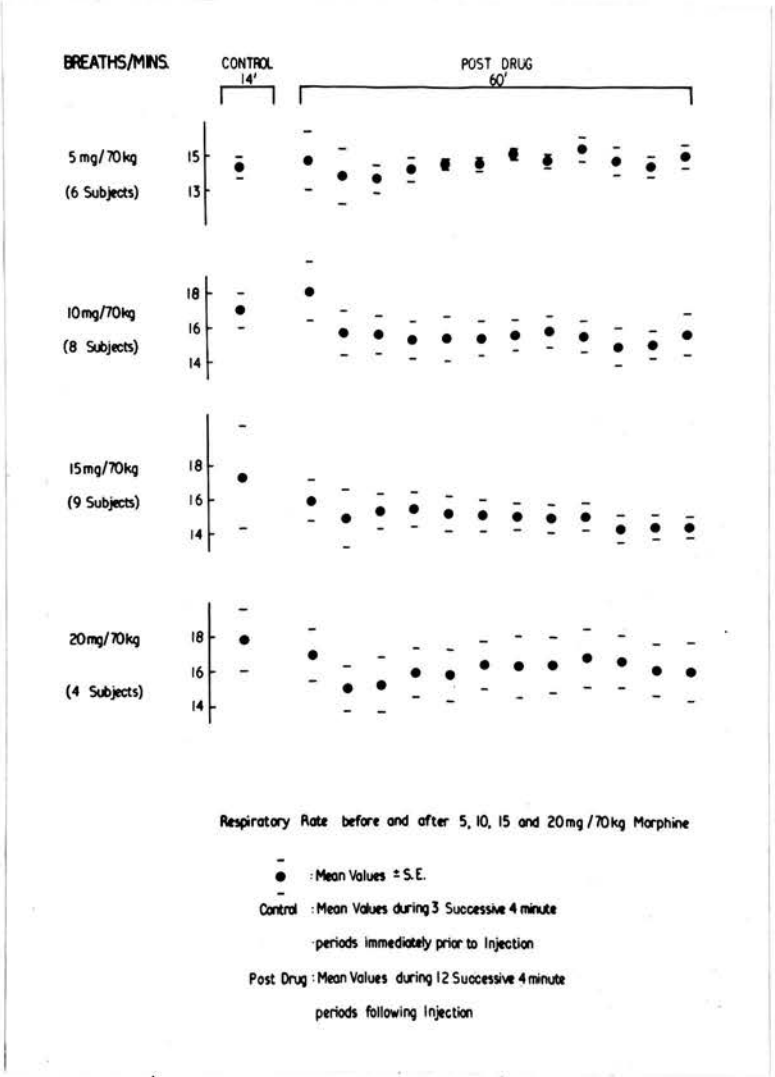

Figure 9

Changes in respiratory frequency (pooled observations) in relation to time after 5, 10, 15 and 20 mg/70 Kg. morphine. Explanations as for Figure 2.

Analysis of variance confirms the existence of a dose effect ($.01 > P > .001$). However, this dose effect disappears when the 5 mg group is eliminated ($P > .2$). The apparently greater effect of 15 mg as compared with 10 mg/70 kg is not significant ($.2 > P > .1$). The effect of 20 mg/70 kg upon the respiratory frequency is apparently less than that of 15 mg although this difference is not significant ($P > .4$). If the changes caused by 10, 15 and 20 mg/70 kg are pooled, the mean depression is significant ($P < .001$).

Thus, doses of morphine in excess of 5 mg/70 kg significantly depress respiratory frequency, but, this effects is not related significantly to the size of dose. By contrast, a dose of 5 mg/70 kg has no significant effect upon respiratory frequency even though it causes significant depression of ventilation.

Changes in Tidal Volume

The changes in tidal volume in relation to time are shown in figure 11. In the 5 mg/70 kg group, there is an initial, though non-significant ($P > .3$) increase which lasts rather longer than the analogous increase in ventilation and respiratory frequency. In the other treatment groups, tidal volume falls immediately after drug administration, appears to recover later in the lo and 15 mg/70 kg groups, but remains depressed throughout the post drug period in the 20 mg/70 kg group.

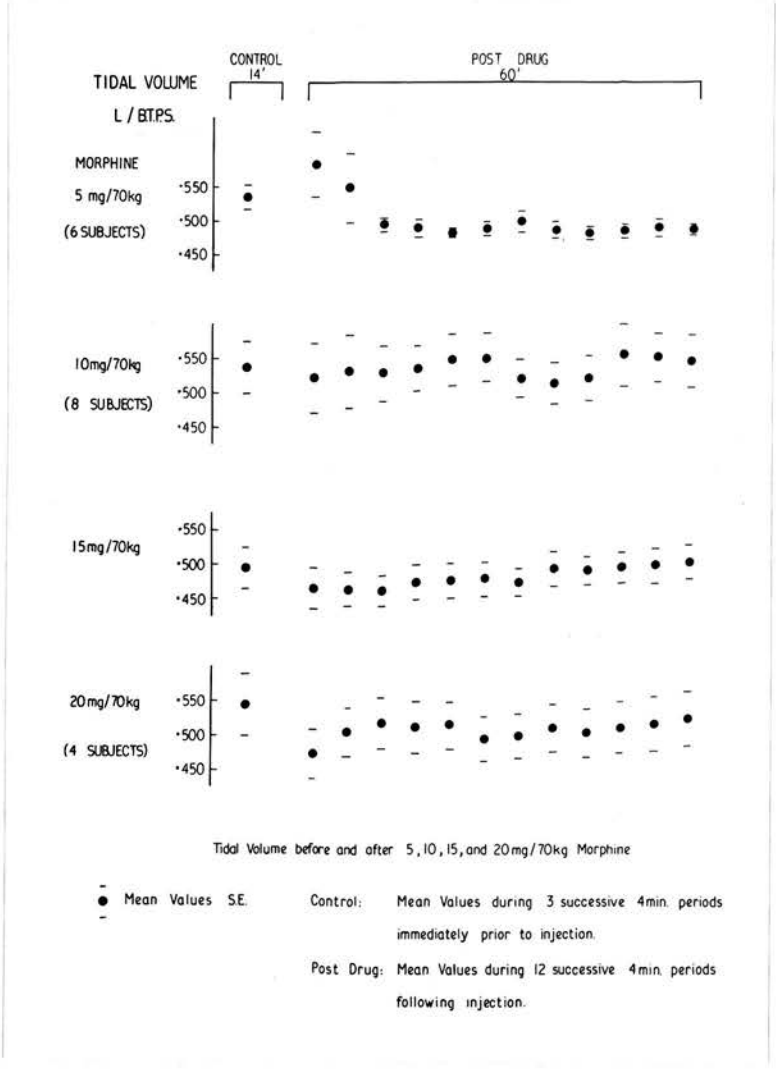

Figure 11

Changes in tidal volume (pooled observations) in relation to time after 5, 10, 15 and 20 mg/70 Kg. (normal subjects). Explanation as in Figure 2.

Over the 60 minute period following drug injection, changes in tidal volume are most clear cut in the 5 and 20 mg/70 kg treatment groups (Tables, 7, 10 and 11).

All four subjects in the 20 mg/70 kg treatment group experienced a significant fall in tidal volume. Of the subjects in the 5 mg/70 kg group, tidal volume rose significantly in 1 and fell in the remaining 5. Among these latter, the depression was significant in 2, just short of significance at .05 level in 1 and non-significant in 1.

The mean fractional depression in the 20 mg/70 kg group was .0667 and, even in so small a group was highly significant ($.01 > P > .001$). The mean fractional depression of .0595 in the 5 mg/70 kg group was not significant ($P = .1$). This is clearly to be attributed to an increase in the mean tidal volume which occurred in the first 9 minutes following injection. When this initial period is excluded from consideration the mean fall in tidal volume in this group is significant ($.05 > P > .02$).

In the 10 and 15 mg/70 kg groups the changes were more variable. In each group the net effect, over the 60 minute post drug period, was a slight mean depression in tidal volume which was, in neither case, significant ($P > .3$ and $> .4$). A significant fall occurred in 2 of 9 subjects in the 10 mg/70 kg group, and in 3 of 9 subjects in the 15 mg/70kg group (Tables 8, 9 and 11). It will be observed that the tidal volume fell in approximately one half of the subjects in these two groups.

The variability of the response in the four treatment groups is considerable, the standard deviation in each group being appreciably larger than the mean value. The effects of 5 and 20 mg/70 kg in depressing tidal volume are nearly equal and considerably greater than the small mean fractional depression of under 2% attributable to the 10 and 15 mg/70 kg doses.

These results would appear to indicate that doses of 5 and 20 mg/70 kg have a very significant tendency to depress the breath volume while this is hardly affected by the intermediate doses. However, analysis of variance and tests between the individual treatment groups show that these apparently differences are not statistically significant (Table 11). This is clearly attributable to the rather large variances. Inspection of the data shows that larger treatment groups would not materially improve the chances of demonstrating statistically significant differences among the treatment groups. Thus, the smallest group numerically, 20 mg/70 kg, exhibits the least variability and the mean depression attains a comfortable level of significance. Further, doses of 10 and 15 mg/70 kg cause, in some subjects, a net increase in tidal volume, thus obscuring, in the pooled calculations, the fall which occurred in other subjects. This source of variability would, presumably, not be removed by any practicable increase in the size of the treatment groups.

If the data in the 4 treatment groups are pooled (Table 11) - a procedure justified by the absence of significant differences - the resulting mean depression in tidal volume of approximately 3% is highly significant

(.01 > P > .001). This indicates that, despite the aforementioned differences, the predominant effect of morphine in all doses used was to depress the volume per breath.

Nevertheless, it seems definite that, in addition to the clearly demonstrable depressant effects, there is a fairly marked tendency for tidal volume to increase after morphine - an effect which is related, in a rather complex manner, to the size of the dose. This tendency is apparent after 5 mg/70 kg, only during the initial 9 minutes of the post drug period; is very marked throughout the greater part of the 10 and 15 mg/70 kg groups; and is at no time apparent in the 20 mg/70 kg group. This mingling of effects could be responsible for the large variances, and, for the failure to demonstrate statistically significant differences among the four treatment groups, despite the apparent existence of such differences. These dose differences appear to be real, even though there is no simple way, such as the use of larger groups, of demonstrating statistically significant differences. However, more detailed dissection of the present data, has, in some measure, surmounted these difficulties.

Inspection of the plotted changes in tidal volume (Figure 11) shows that, immediately after drug administration, the mean tidal volume rises in the 5 mg/70 kg group and falls in the other groups. In the 10 and 15 mg/70 kg treatment groups, this depression in tidal volume lasts for some 19 minutes following which a gradual recovery supervenes. In the 20 mg/70 kg group, the tidal volume, though showing some tendency to fluctuate, remains depressed throughout the post drug period. It therefore appears that the

initial effect of doses larger than 5 mg/70 kg is to depress the tidal volume, at any rate for some 19 minutes following drug administration. Consequently, the changes in each treatment group occurring during the first 4, 9, 14 and 19 minutes after drug administration have been separately analysed, in the usual manner, by treating the individual differences as normally distributed variables, with the following results (Table 14).

The depression in tidal volume occurring during the initial 4 minute period is significant in the 20 mg/70 kg group ($.05 > P > .02$), is short of the .05 level of significance in the 15 mg/70 kg group ($.1 > P > .05$) and not significant in the 10 mg/70 kg group ($p > .2$). The increase noted, at the same time, in the 5 mg/70 kg group is not significant ($P > .3$). Analysis of variance shows a just significant dose effect ($P = .05$) which disappears after removal of the 5 mg/70 kg group ($.2 > P > .1$), although the result suggests that a rather weak dose effect might be present.

Further analysis of the changes at 9, 14 and 19 minutes post drug yields very similar results. The depression in tidal volume at these times, in the 15 and 20 mg/70 kg groups is significant, while the changes in the 5 and 10 mg/70 kg groups are not. Again, the depression in tidal volume appears with the dose administered, but, this apparent dose effect is not significant ($.2 > P > .1$). The variability in the 5 and 10 mg/70 kg groups particularly is considerable, mainly, because of the increase in tidal volume which occurs in some subjects.

These results may, therefore, be interpreted as follows. The predominant effect of the drug on tidal volume, in the doses administered, is depressant, and, this effect increases with the size of the dose. In addition, the opposite effect, that is, a tendency to increase the breath volume, is also present. Both effects occur in each of the treatment groups. In the 5 mg/70 kg group the stimulatory effects are most prominent during the initial 9 minutes of the post drug period. In the remaining groups, the depressant effects can be shown to be predominant during the initial 19 minutes of the post drug period. Presumably, both effects are present in all the treatment groups throughout the post drug period. Although this could not be rigorously demonstrated, both effects are almost certainly related to dose. Thus may be explained the paradox that 5 and 20 mg/70 kg are equally effective in depressing the volume per breath.

Later, it will be shown that the effects of the drug in oxygen consumption are rather similar to those on tidal volume, encompassing a mixture of depressant and stimulatory effects. It is very probable that changes in tidal volume and changes in oxygen consumption are indeed linked.

Effect on Oxygen Consumption

The movements of oxygen consumption in relation to time are shown in figure 12. An immediate increase in oxygen consumption followed by a fall to values somewhat below control levels, occurs in the 5 and 10 mg/70 kg groups. To a considerable extent, the changes in these two groups mirror the corresponding movements in tidal volume. The immediate effect in the

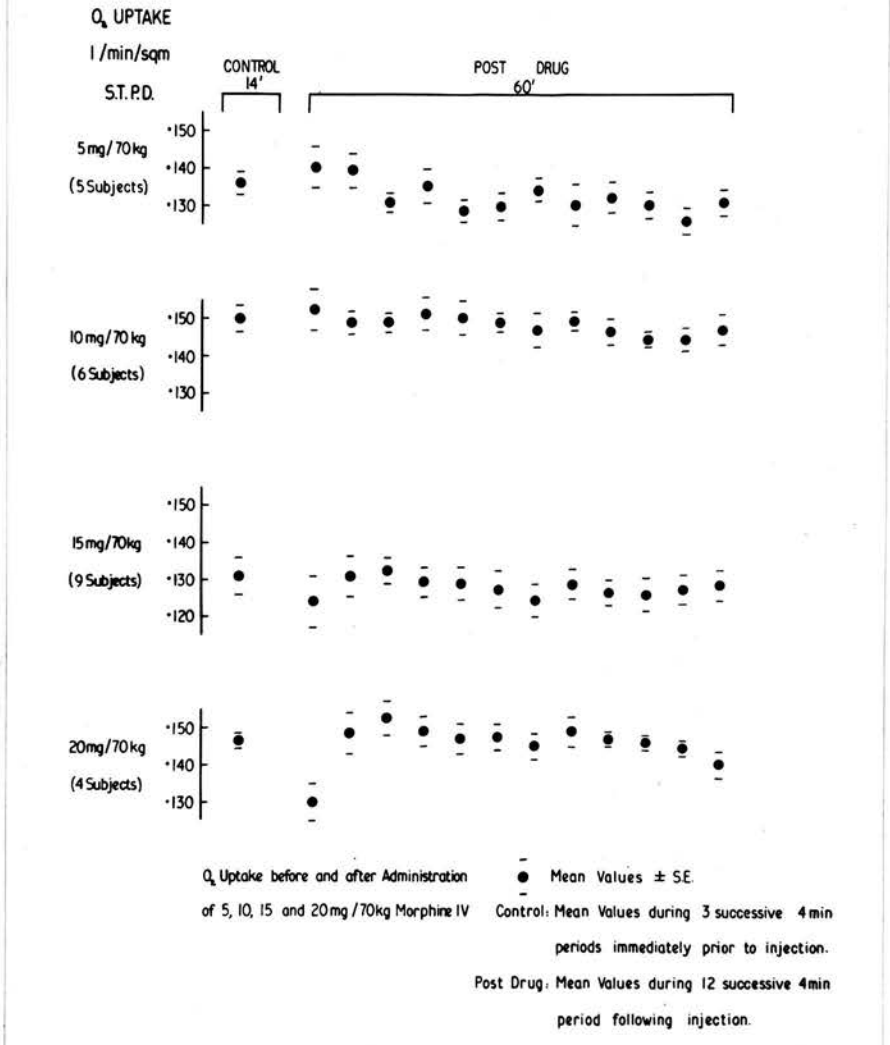

Figure 12

Changes in O_2 uptake (pooled observations) in relation to time after 5, 10, 15 and 20 mg/70 Kg. (Normal subjects). Explanation as in Figure 2.

15 and 20 mg/70 kg groups is a sharp fall in the mean value for oxygen uptake followed by a rather rapid recovery to values which are somewhat below the control levels.

A significant depression in oxygen uptake, in individual subjects, was rather uncommon. No individual in the 20 mg/70 kg group experienced such a fall; two subjects in each of the remaining groups did so. A significant increase in oxygen uptake occurred in one subject in the 10 mg/70 kg group, and non-significant increases occurred in 2 and 4 subjects in the 10 and 15 mg/70 kg groups respectively, and in 2 subjects in the 20 mg/70 kg group (Tables 7 - 10, figure 13).

In each treatment group there was a very modest mean decline in oxygen uptake varying from less than 1% in the 20 mg/70 kg group to 2.5% in the 5 mg/70 kg group (Table 11). This change is significant only in the 5 mg/70 kg group ($.05 > P > .02$). Among 21 subjects in the 10, 15 and 20 mg/70 kg groups, 9 experienced a net increase in oxygen consumption over the 60 minute post drug period - a feature which contributes to the very marked variability of response such that the standard deviations are appreciably larger than the means.

Analysis of variance on these data shows no evidence of a dose effect, the mean square within being greater than the mean square between the treatment groups though not significantly so ($.1 > P > .05$). This finding would appear to point to the existence of some important influence operating within the treatment groups. These observations do not, of course, prove that the size of dose is unrelated to the effect of the drug on oxygen consumption

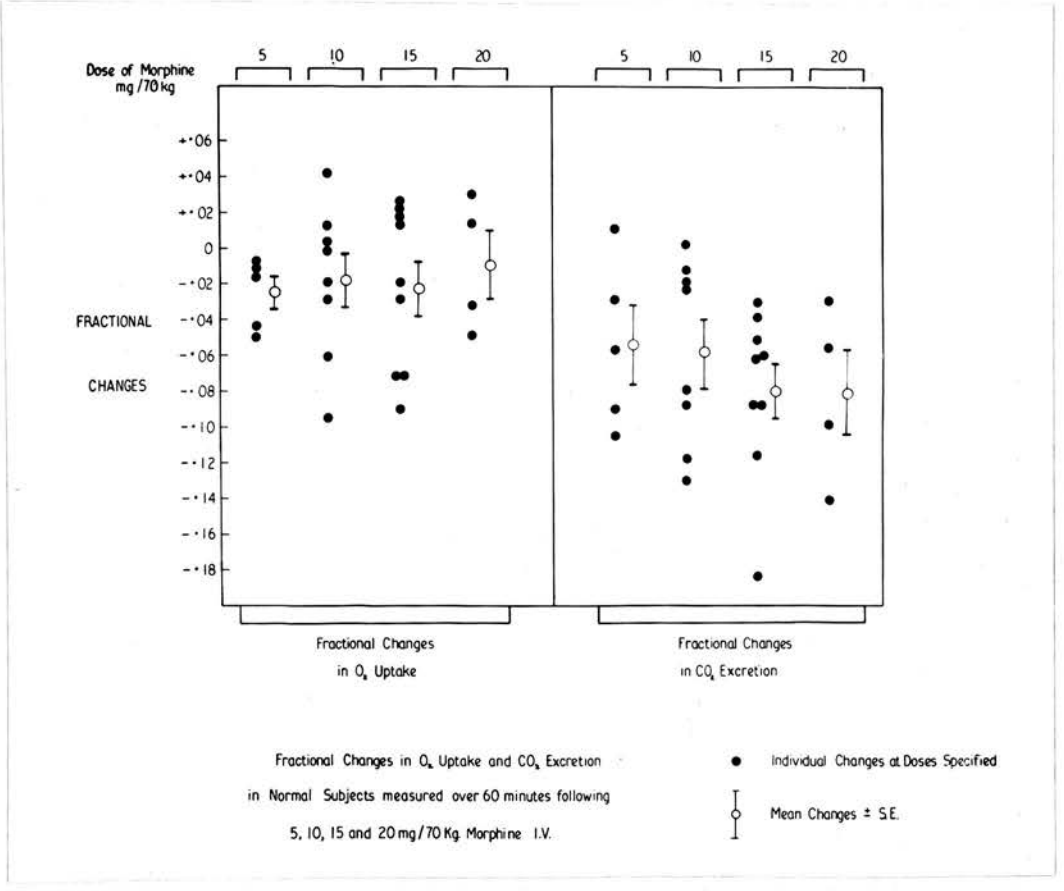

Figure 13

Fractional changes in O_2 uptake and CO_2 output after 5, 10, 15 and 20 mg/70 Kg (normal subjects), measured over the 60 minute post-drug period. Individual values and mean values ± S.E. for each group are shown.

but rather suggest that there are factors operating within the treatment groups to submerge any such dose effect which may exist.

If the data relating to the four treatment groups are pooled - a valid procedure since the differences are not significant - the resultingsmall mean depression of approximately 2% is significant ($.02 > P > .01$) (Table 11). This shows that the predominant effect of the drug upon oxygen uptake is depressant at any level of dose used in the present study.

A linear relationship exists between oxygen consumption and minute ventilation both during the control period and that following drugadministration (figures 14A, 14). Rather surprisingly, however, changes in oxygen uptake do not correlate significantly with changes in ventilation ($r = .224$, $n = 26$, figure 15). The common regression line derived by covariance analysis has a non-significant slope, ($.1 > P > .05$), the equation being :

$$\text{Fractional changes in oxygen uptake} = .0133 + (.2898 \pm .1619) \times \text{Fractional changes in ventilation} \quad (1)$$

The standard deviation around the regression line is .0382.

While it is likely that a larger number of observations would have yielded a significant slope, the results do suggest that the drug may have caused changes in oxygen uptake entirely independent of its effects on ventilation.

Since oxygen uptake and ventilation are linked, the changes in the former have been further studied by comparing the control and post drug regression lines relating these two variables. Mean values for oxygen uptake and ventilation during the control period have been plotted for 31

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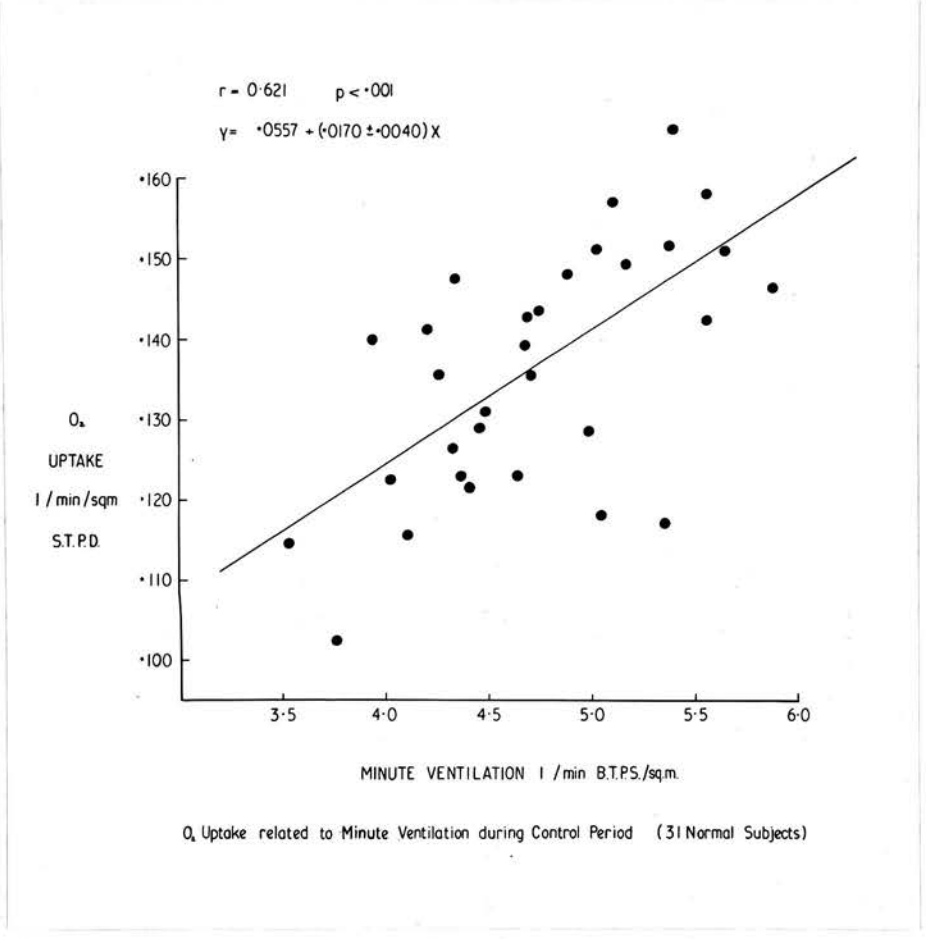


O_2 Uptake related to Minute Ventilation during Control Period (31 Normal Subjects)

Figure 14a

Fitted regression line - O_2 uptake related to ventilation (mean control values in 31 normal subjects).

$$\dot{V}_{O_2} = .0557 + (.0170 \pm .0040)\ \dot{V}_E$$

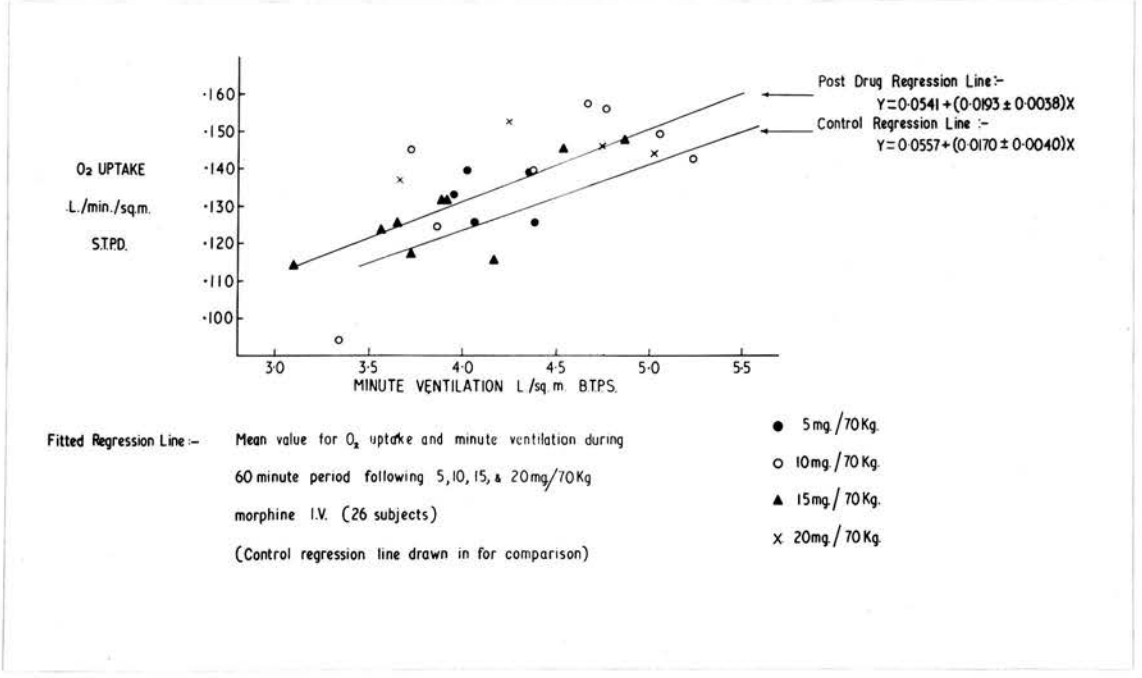


Figure 14

Fitted regression line - O_2 uptake related to ventilation (mean values over 60 minute period following 5, 10, 15 and 20 mg/70 Kg. morphine in 26 normal subjects).

$$\dot{V}_{O_2} = .0541 + (.0193 \pm .0038) \quad \dot{V}_E$$

Control regression line (Figure 14a) drawn in for comparison.

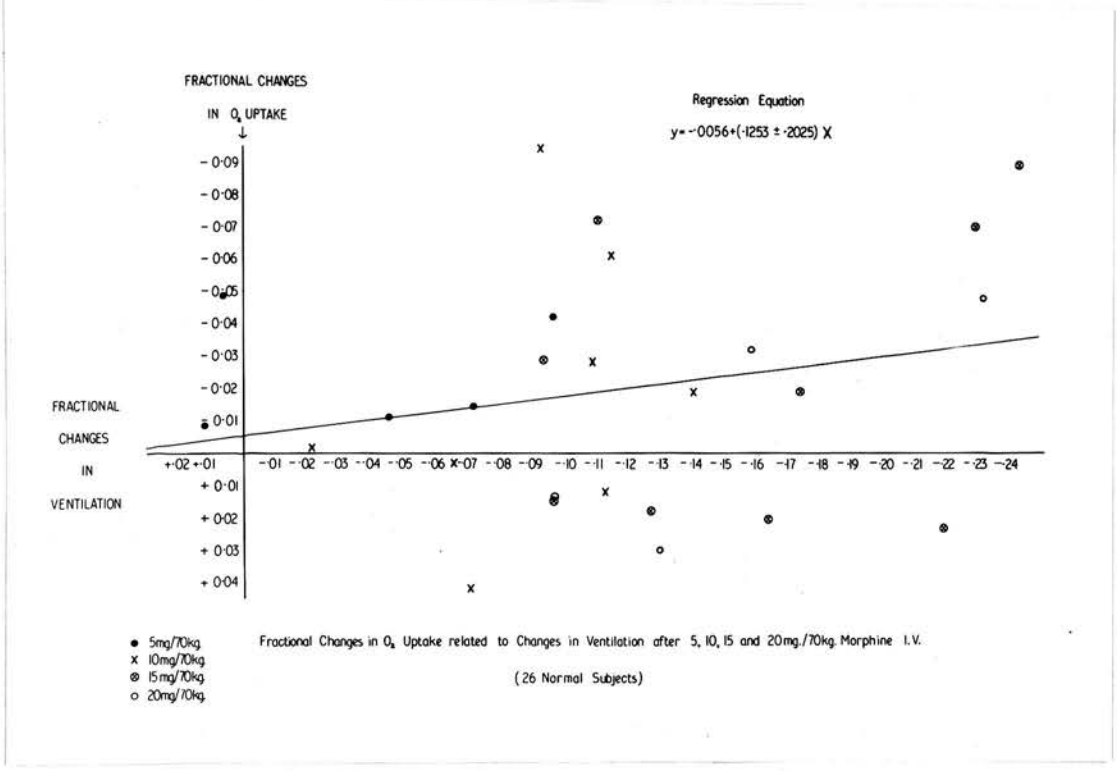


Figure 15

Fitted regression line. (total regression). Fractional changes in O_2 uptake related to changes in ventilation.

Fractional changes

$$\dot{V}_{O_2} = .0056 + (.1253 \pm .2025) \times \text{fractional change in } \dot{V}_E$$

The regression derived by covariance analysis (see text) is probably a better estimate than the above and somewhat closer to significance.

normal subjects. These include the subjects in the four groups treated with morphine, 4 subjects in the phenobarbitone group and one subject in whom the study was abandoned after the control data had been collected. The mean paired values for oxygen uptake and ventilation over the entire post drug period have been similarly plotted for the 26 subjects given morphine (figures 14A,14). Both slopes are positive and significant ($P < .001$). They are not significantly different from one another. It is to be noted, however, (figure 14) that the regression line fitted to the post drug observations lies above the control line. Formal testing of the difference between the adjusted means ($.0086 \pm .0035$) confirms that the elevation of the post drug regression line is significantly greater than that of the control line ($.05 > P > .02$). Thus, after administration of morphine, a given level of ventilation is apparently associated with a larger oxygen uptake than during the control period. These observations mean, that, independent of its depressant effects upon ventilation, the drug simultaneously increases oxygen uptake. The difference between the adjusted means suggests that this effect upon metabolism is an appreciable one.

*(1) The estimates of correlation co-efficient ($r = .364$) and slope derived by this method are rather closer to significance than the statistics used in figure 15.

The parameters which estimate these regressions are given below :

Regression	r	Degrees of freedom	S_{yx}	$\bar{Y}$	a + (b ± S.E.)	$\bar{X}$
Control	.621	29	.0128	.1358	.0556 + (.0170 ± .0040)	4.723
Post drug	.721	24	.0105	.1347	.0541 + (.0193 ±.0038)	4.184

The relationship between the dose of morphine and the apparent increase in oxygen uptake which the drug causes will now be considered, and, for this purpose also, the methods of regression analysis are very suitable. The above mentioned regression lines are not, however, efficient instruments for this purpose. Consequently, the following method has been used. In each treatment group, common regression lines have been derived by co-variance analysis in respect to the control and post drug periods separately. This technique makes it possible to consider, in each group separately, any differences which arise between the control and post drug regression lines relating oxygen consumption and ventilation and thus to separate the presumed effects of each dose of morphine upon oxygen uptake from those upon ventilation.

For the derivation of the common control regression the 5 paired observations of oxygen uptake and minute ventilation for each subject have been used. In estimating the common post drug regression the initial 3 paired observations have been excluded from the calculations because of the marked instability in ventilation and oxygen uptake which is, at that time, present in many subjects. The removal of these initial observations has been found

by trial and error, to lead to more satisfactory treatment of the data because of the disappearance, after such removal, of much of the variability between individual subjects. This procedure, however, involves the disadvantage that the conclusion of this analysis are applicable only to the latter 45 minutes of the post drug period - a limitation found in practice not to be significant.

The results of this analysis will now be considered in detail (Table 12, figures 16 - 19). In respect to the control regressions, there are evidences of significant slope differences between subjects, only in the 15 mg/70 kg group ($.025 > P > .01$). There is no satisfactory method of removing this heterogeneity and, in consequence, the derived common estimate of slope has been accepted as the best available and as suitable for present purposes. The treatment groups show significant differences in slope among themselves ($.025 > P > .01$) - a finding which emphasises the importance of estimating a separate control slope for each treatment group. As a matter of interest and as an illustration of the linear relationship which exists between oxygen uptake and ventilation under the very stable conditions of the control period, the common regression derived by pooling all treatment groups is given (Table 15).

The post drug regressions show no evidence of significant slope differences between subjects in any of the four treatment groups. However, the treatment groups show significant slope differences ($.05 > P > .025$).

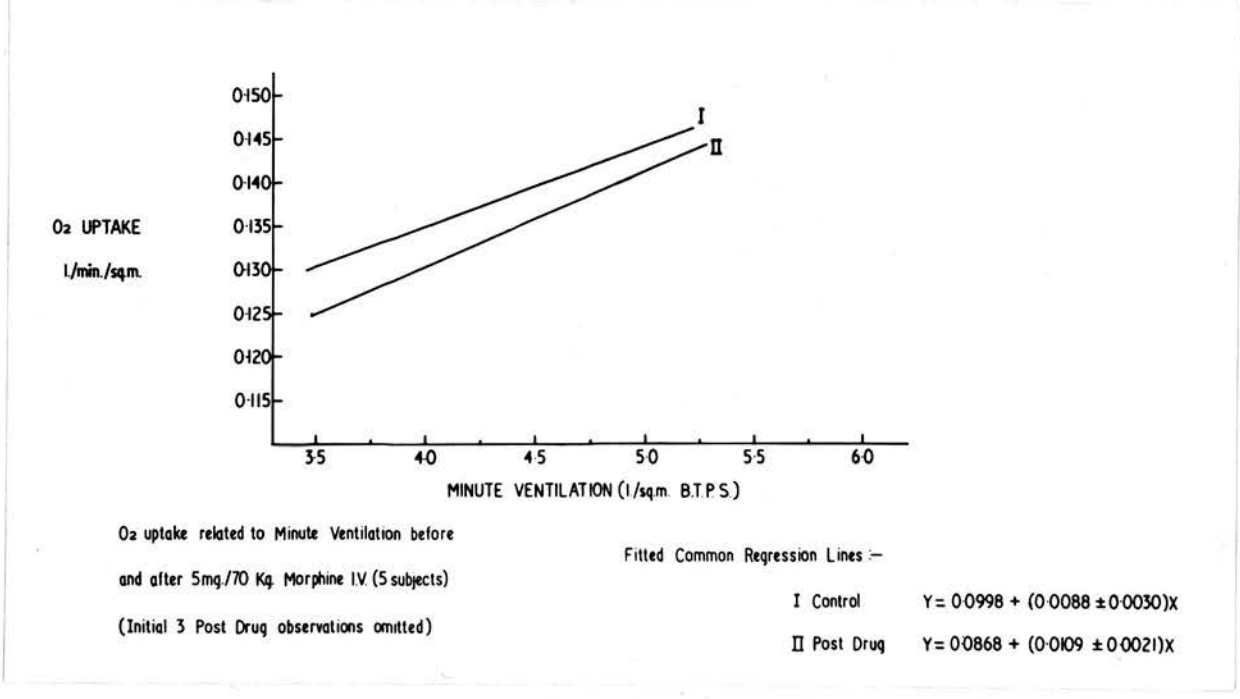


Figure 16

Fitted regression lines (common lines derived by covariance analysis) - O_2 uptake related to ventilation before and after 5 mg/70 Kg. morphine (initial three post-drug observations excluded from computations) - normal subjects.

I Control $\dot{V}_{O_2} = .0998 + (.0088 \pm .0030)\,\dot{V}_E$

II Post-drug $\dot{V}_{O_2} = .0868 + (.0109 \pm .0021)\,\dot{V}_E$

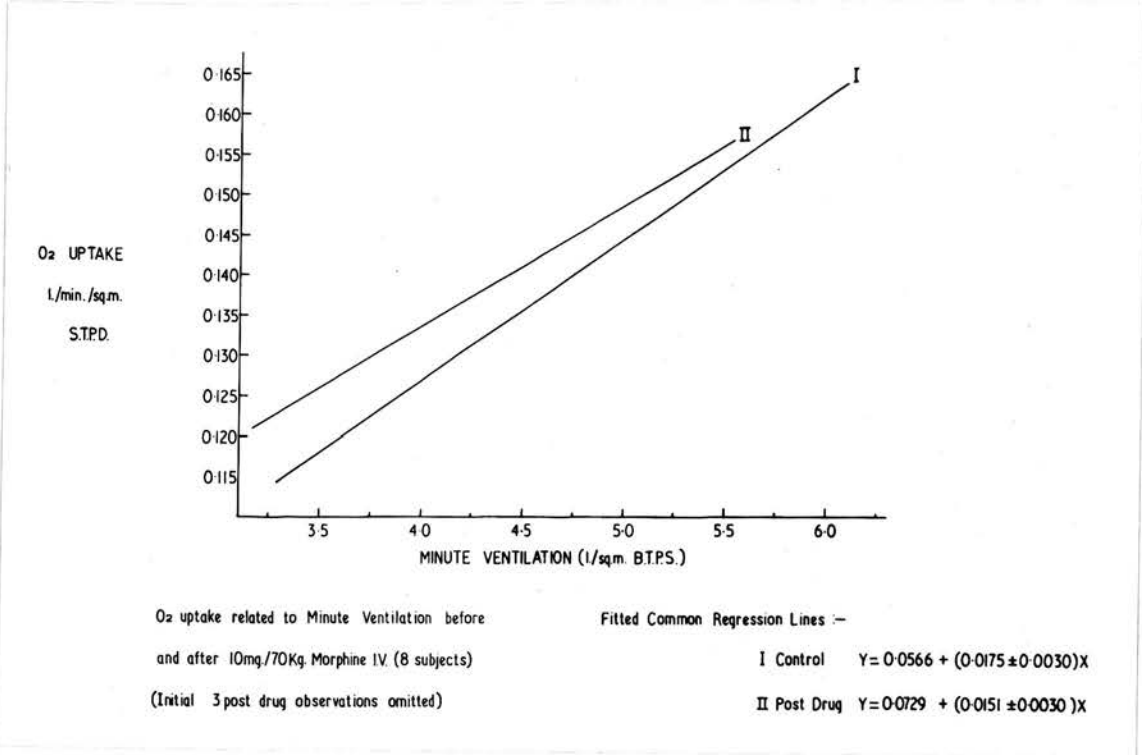


Figure 17

Fitted regression lines (common lines derived by covariance analysis) - O_2 uptake related to ventilation before and after 10 mg/70 Kg. morphine (initial three post-drug observations excluded from computation) - normal subjects.

I **Control** $\dot{V}_{O_2} = .0566 + (.0175 \pm .0030)\,\dot{V}_E$

II **Post-drug** $\dot{V}_{O_2} = .0729 + (.0151 \pm .0030)\,\dot{V}_E$

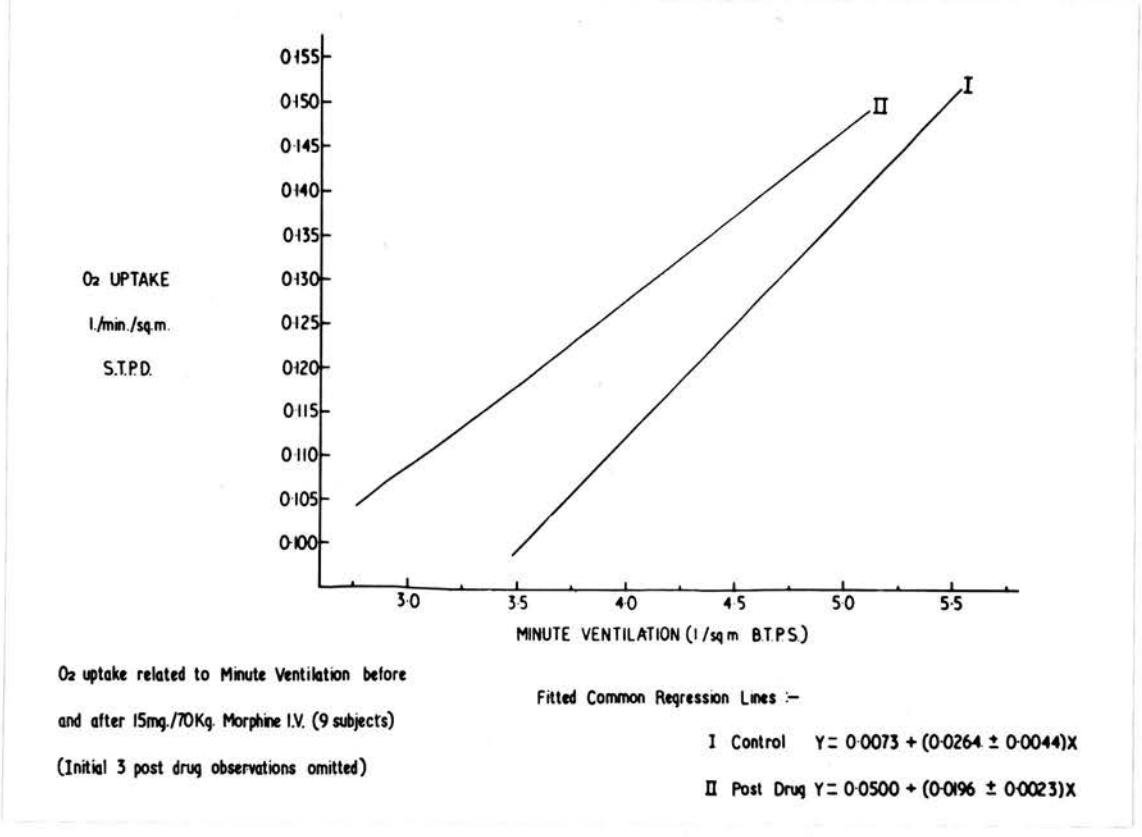
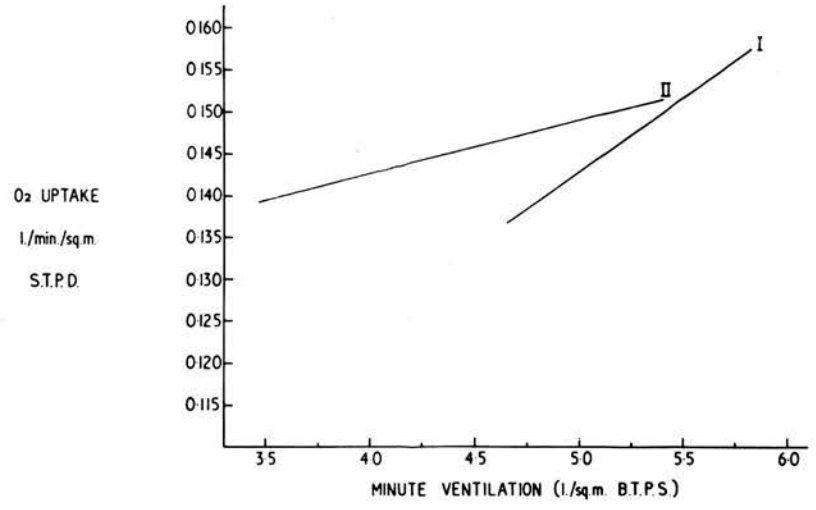


Figure 18

Fitted regression lines (common lines derived by covariance analysis) - O_2 uptake related to ventilation before and after 15 mg/70 Kg. morphine (initial three post-drug observations excluded from computation) - normal subjects.

$$\text{I} \quad \text{Control } \dot{V}_{O_2} = .0073 + (.0264 \pm .0044)\,\dot{V}_E$$

$$\text{II} \quad \text{Post-drug } \dot{V}_{O_2} = .0500 + (.0196 \pm .0023)\,\dot{V}_E$$



O2 uptake related to Minute Ventilation before and after 20 mg./70 Kg. Morphine I.V. (4 subjects)
(Initial 3 Post Drug periods omitted)

Fitted Common Regression Lines :—

I Control $Y = 0{\cdot}0539 + (0{\cdot}0178 \pm 0{\cdot}0050)X$

II Post Drug $Y = 0{\cdot}1176 + (0{\cdot}0063 \pm 0{\cdot}0052)X$

Figure 19

Fitted regression lines (common lines derived by covariance analysis) - O_2 uptake related to ventilation before and after 20 mg/70 Kg. morphine (initial three post-drug observations excluded from computation) - normal subjects.

$$\text{I} \quad \text{Control} \quad \dot{V}_{O_2} = .0539 + (.0178 \pm .0050)\ \dot{V}_E$$

$$\text{II} \quad \text{Post-drug} \quad \dot{V}_{O_2} = .1176 + (.0063 \pm .0052)\ \dot{V}_E$$

The four control slopes and the post drug slopes with the exception of that of the 20 mg/70 kg group (.3 > P > .2), are significant.

When each post drug regression line is compared with its control the findings are as follows (Table 15, figures 16 - 19). There is no significant slope difference between the control and post drug regressions in any of the four treatment groups. The post drug slope of the 20 mg/70 kg group is, however, not significant. In the 5, 10 and 15 mg/70 kg groups, the elevations of the two regression lines are significantly different. The 5 mg/70 kg post drug line is significantly depressed, the 10 and 15 mg/70 kg post drug lines are significantly elevated, as shown by the significant differences between the adjusted means. Because of the non-significant slope of the 20 mg/70 kg regression, it is doubtful whether it is justifiable to test for a significant difference between the adjusted means. Nevertheless, inspection of the curves shows that, not only is this slope flattened, but the line itself is displaced upwards, so that the effect of this dose is directionally similar to that of 10 and 15 mg/70 kg and perhaps more marked. The difference between the adjusted means, however, is not significant (P > .5).

The results of this analysis show conclusively that, independent of any effect on ventilation, a dose of 5 mg/70 kg depresses, and doses of 10, 15 and 20 mg/70 kg increase oxygen uptake. Thus morphine is clearly shown to be a metabolic stimulant in man when administered in doses within the

ordinary therapeutic range: that this effect increases with increasing dose: that it is quite marked and lasts throughout the post drug period of observation in the 10, 15 and 20 mg/70 kg groups. After a dose of 5 mg/70 kg, the stimulant effects upon oxygen uptake are apparently restricted to the early post drug period.

This stimulant effect upon oxygen uptake must therefore be regarded as an independent effect occurring pari passu with the depressant effect which, the regression relationship indicates, must necessarily accompany the decline in minute ventilation recorded in all treatment groups. It is, further, interesting that an independent depressant effect upon oxygen consumption can be shown to have occurred during the later post drug period in the 5 mg/70 kg group. In this last named group, the stimulant effect upon oxygen uptake is restricted to the early post drug period, when it is associated, even though for a very brief period, with a fairly marked increase in ventilation. Presumably these independent depressant effects are due to "sedative" or other central depressant action of the drug and may well exist also in other treatment groups. Unfortunately, there is no available method of analysis which will uncover this effect. However, it is rather attractive to speculate that the sharp initial decline in oxygen uptake which regularly occurs after doses of 15 and 20 mg/70 kg (figure 12) at a time when ventilation is changing less dramatically, represents a central depressant effect upon metabolism which is later obscured by the more potent stimulant effects.

The effects of morphine, as administered in the present study, upon oxygen uptake, may be summarised as follows. Over the 60 minute period following intravenous administration, the net effect of the drug, in the series considered as a whole is to cause a small but significant fall in oxygen uptake. There are no significant differences between the four treatment groups in respect to this depression in oxygen uptake, although paradoxically the fall is significant only in the group treated with 5 mg/70 kg. More detailed analysis shows that morphine affects oxygen uptake in three ways.

First, the drug causes a fairly marked increase in oxygen uptake, independent of any effects on ventilation, in the 10, 15 and 20 mg/70 kg groups. In the 5 mg/70 kg group, this effect is limited to the early post drug period, when for a very brief part of this period,there is an associated marked increase in ventilation. The stimulant effect upon metabolism is appreciable and has been shown to be directly related to the dose administered.

Secondly, the drug depresses oxygen uptake because of its depressant effects upon ventilation. The present study has demonstrated conclusively that, within the range of ventilation studied, both during control and post drug periods, a linear relationship exists between oxygen uptake and ventilation. Consequently, changes in the one, will of necessity, produce changes in the other.

Thirdly, the drug depresses oxygen uptake, independently of its depressant effects upon ventilation and this is, presumably, related to its sedative and other central effects. Such a depression can be shown by direct analysis of the date to have occurred only in the group which received 5 mg/70 kg after the initial period of metabolic stimulation had ended. In this group, as judged by the depression of the post drug regression line, this depressant effect upon oxygen uptake appears to be fairly marked. Presumably, this effect occurred also in the treatment groups which received larger doses, although this could not be shown directly to have occurred, on the available data. It is possible that the initial sharp and very transient fall in oxygen uptake which regularly occurs in the 15 and 20 mg/70 kg groups may represent an independent metabolic depressant effect.

This mingling of effects, each with its own relationship to the size of dose, no doubt explains why direct comparisons of changes in oxygen uptake do not show significant dose effects, and, also, the paradox that a dose of 5 mg/70 kg is more regularly effective in depressing oxygen uptake that larger doses.

Changes in Carbon Dioxide Excretion

The effects of morphine on carbon dioxide excretion will be presented and analysed in a manner similar to that used in the preceding section.

The charts (figure 20) indicate that in the 5 and 10 mg/70 kg groups the mean carbon dioxide output rose sharply immediately following drug administration before a sustained fall to values well below control levels occurs. This initial increase was slightly more marked in the 5 mg/70 kg group. In the 15 and 20 mg/70 kg groups, the carbon dioxide output fell sharply immediately after injection and though recovering slightly, remained depressed below control values for the remainder of the experiment.

Individual subjects nearly always experienced a fall in carbon dioxide output after morphine. One subject each in the 5 and 10 mg/70 kg groups showed a small, non-significant increase in carbon dioxide output. Of the remaining subjects, 13 showed a significant and 11 a non-signficant decline in carbon dioxide output (Tables 7 - 10). The highest proportion of subjects showing a significant fall occurred in the 15 mg/70 kg group - 6 of 9 subjects in this treatment group experienced such a fall. In the remaining groups, there was a significant decline in carbon dioxide output in approximately 50% of subjects.

The mean fall in carbon dioxide output was, in each treatment group, statistically significant (Table 11). The decline in carbon dioxide output shows an apparent slight relationship to the dose administered. However, analysis of variance fails to demonstrate any significant differences among the treatment groups, and the slope of the regression line relating changes

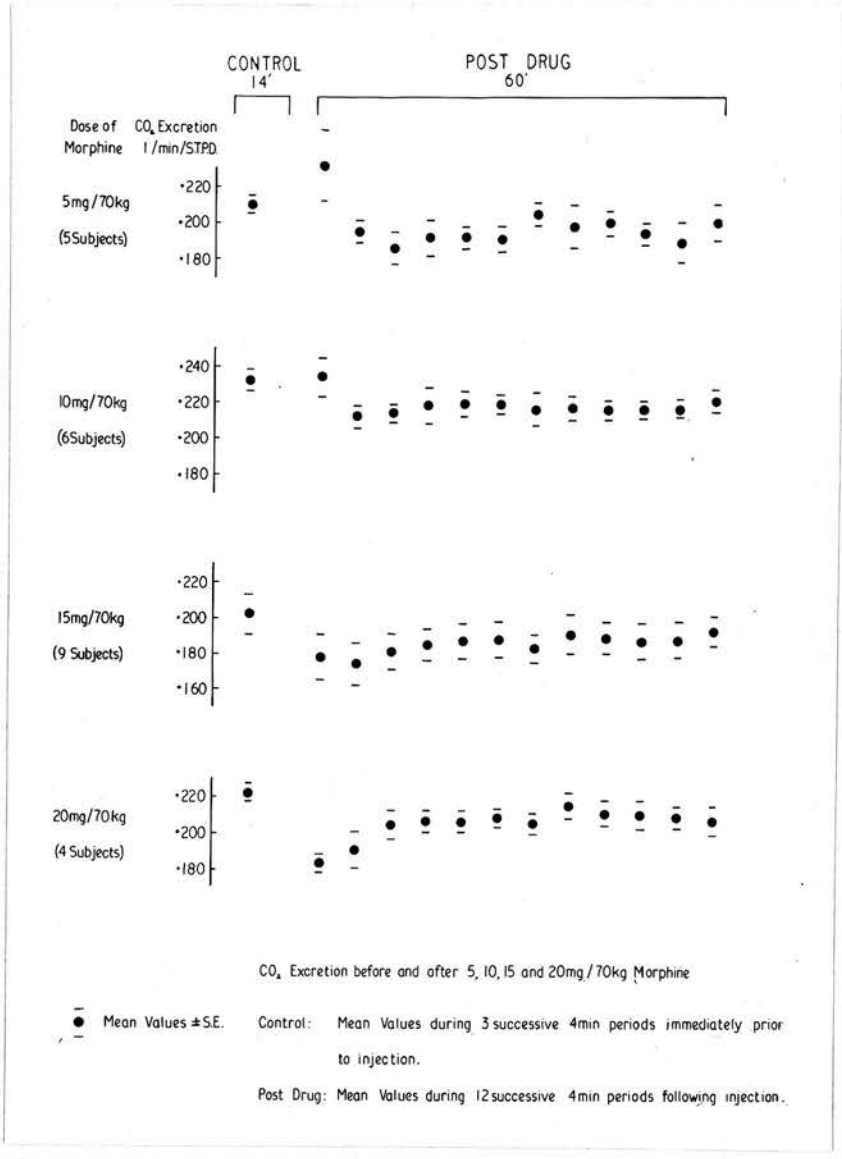


Figure 20

Changes in CO_2 output (pooled observations) in relation to time after 5, 10, 15 and 20 mg/70 Kg. morphine - normal subjects. Explanations as in Figure 2.

in carbon dioxide output to dose of drug is not significant (-.0023 ± .0019 n = 26, P > .2). It is to be noted that variation within the treatment groups is rather marked, the standard deviation being approximately equal to the mean in the 5 and 10 mg/70 kg groups and over 50% of the mean in the 15 and 20 mg/70 kg groups.

The causes of these changes in carbon dioxide output will now be considered.

The fractional changes in carbon dioxide output have been considered, by the use of regression analysis, in relation to changes in ventilation and oxygen uptake. Fractional changes in carbon dioxide output are linearly related to changes in ventilation, and, also, to changes in oxygen uptake. Common slopes derived, in the usual way by covariance analysis, are significant ($P < .001$ for both slopes) and the tests show that there are no significant slope differences among the four treatment groups. Thus, the relationship between changes in carbon dioxide output and changes in ventilation and oxygen uptake is not affected by the dose administered. The regression equations derived in this manner are as follows:

Fractional changes in CO_2 output = .0037 + (.6323 ± .1609) x change in ventilation

" " " " " = -.0500 + (.9412 ± .1640) x change in oxygen uptake

The standard deviation about the regression lines are .0380 and .0308 respectively.

It seemed desirable to calculate partial regression constants for linking these threevariables in one equation. The partial regression constants so calculated (using the pooled sums of squares) are, in each case, highly significant ($P < .01$ and $< .001$ respectively). The fitted regression line has the equation :

$$\text{Change in } CO_2 \text{ output} = -.0063 + (.4143 \pm .1188) \times \text{change in ventilation} + (.7519 \pm .1491) \times \text{change in } O_2 \text{ uptake}$$

The standard deviation about the regression line is .0261.

Thus, following administration of morphine, changes in carbon dioxide output are related to changes in ventilation and, independently, to changes in oxygen uptake. It will be apparent from the above regression constants that the dependence upon changes in oxygen uptake is considerably the more marked. Since, as demonstrated in the previous section, changes in oxygen uptake are only slightly and, non-significantly in the statistical sense related to changes in ventilation, it is not surprising that the changes in carbon dioxide output following drug administration are not significantly related to the size of dose. It seems reasonable to presume that the relationship to the size of dose has been attenuated by the above multilateral relationships.

Carbon dioxide output and ventilation are linearly related (figure 21). This relationship is rather closer than that which exists between oxygen uptake and ventilation, so that about 70% of the variation in carbon dioxide

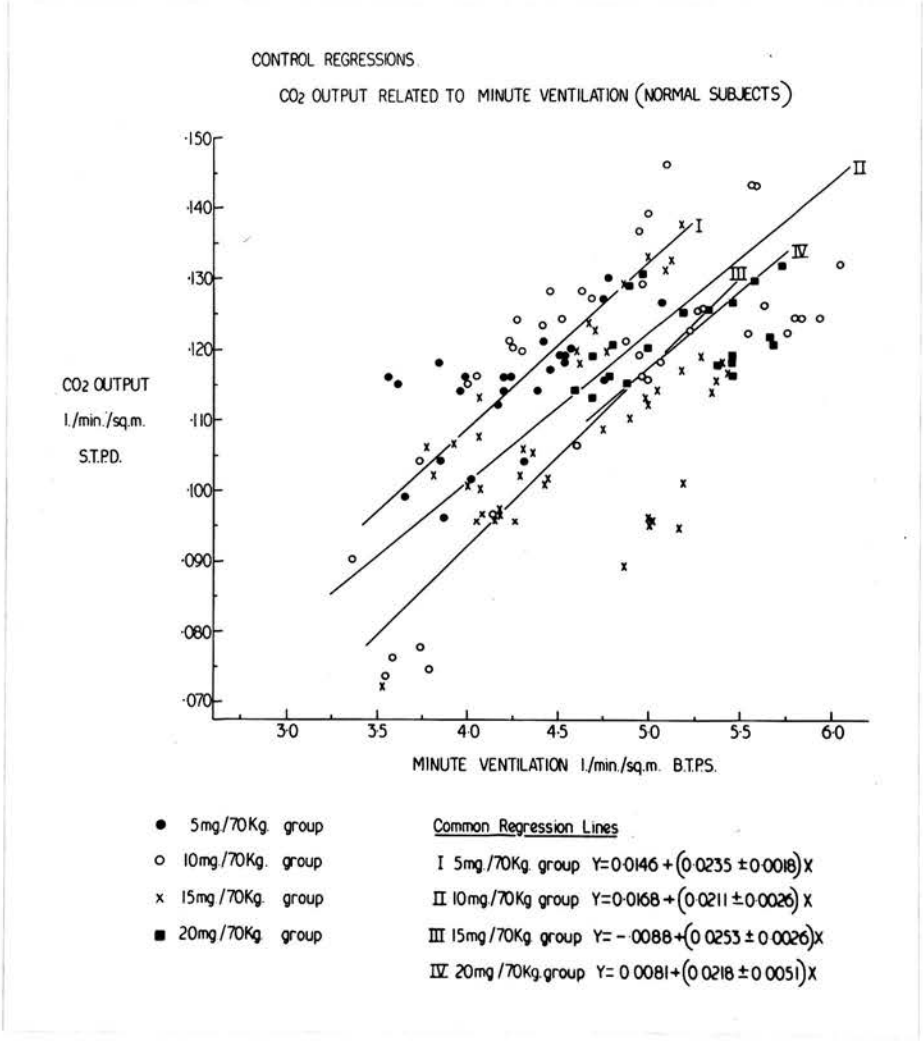


Figure 21

Fitted regression lines (common lines derived by covariance analysis) - CO_2 output related to ventilation during control period - all normal morphine treatment groups.

output during the control period is to be attributed to variation in ventilation. The changes in carbon dioxide will be further considered, as were changes in oxygen uptake, by regression analysis. The regression considered will be that of carbon dioxide output on ventilation, mainly because the movement of oxygen consumption has also been considered previously in relation to ventilation. No doubt CO_2 output /O_2 uptake regression would be equally efficient and, probably would lead to the same conclusions.

In each treatment group, CO_2 output/ventilation regressions have been derived separately for control and post drug periods by covariance analysis in the usual way. The changes in regression, if any, caused by each dose used and, thus, any effects upon carbon dioxide independent of effects on ventilation, could then be considered.

The control slopes derived in this way have usually shown significant slope differences among the individual subjects (Table 16). Only the 15 mg/70 kg treatment group is homogenous in this respect. No acceptable method of removing this heterogeneity of slope could be found and the derived common slopes have been accepted as the best estimate available. The treatment groups show no evidence of significant differences among themselves in the slopes so derived. These slopes, are numerically very close to each other, and are believed to be satisfactory estimates of slope for the purposes of this analysis.

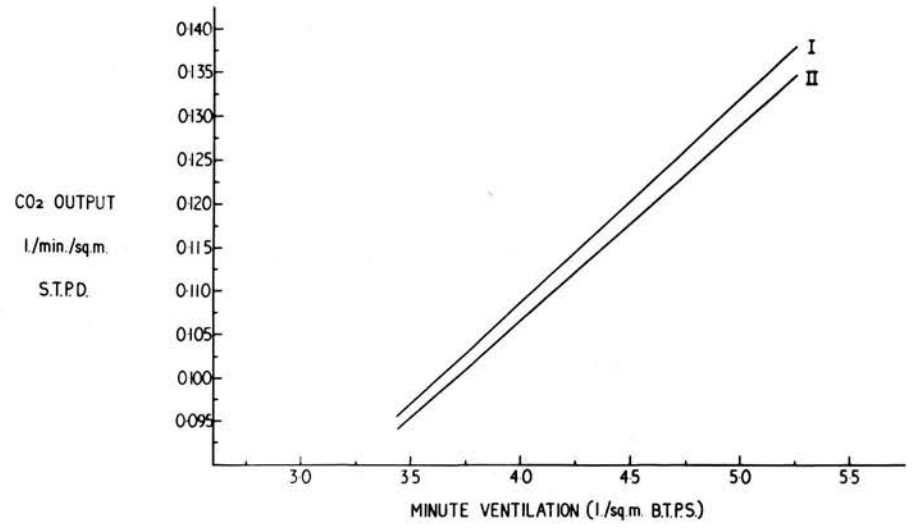
The post drug regressions, similarly derived, and omitting the initial 3 paired observations, for reasons previously given, also usually show

significant slope differences among the individual subjects. Only the 5 mg/70 kg group is homogenous in this respect. There are no significant differences among the treatment groups in respect to the slopes so derived. These slopes also are considered satisfactory for the purposes of the present study. It will be noted that the pooled estimate of post drug slope is numerically very close to that of the control slope.

All slopes, control and post drug, are significant.

In each treatment group, the control and post drug slopes are not significantly different and, except in the 20 mg/70 kg group, numerically are very close. However, in each treatment group, the test of adjusted means show that the control and post drug elevations differ significantly. These changes are directionally identical with those previously noted when oxygen consumption was similarly studied. Thus, the 5 mg/70 kg post drug regression line is significantly depressed and the 10, 15 and 20 mg/70 kg regression lines are significantly elevated, as compared with the control line (Table 16, figures 22 - 25).

These results would appear to indicate quite conclusively that morphine affects carbon dioxide output, as it does oxygen consumption, independent of ventilation. Thus, 5 mg/70 kg depresses, and the other doses increase carbon dioxide output independent of any changes in ventilation during the latter 45 minutes of the post drug period of observation. Consequently, morphine depending on the dose used, is both a depressor and a stimulant to endogenous carbon dioxide formation. The stimulant effects increase with increasing dose, at any rate, up to 15 mg/70 kg.



CO_2 output and ventilation before and after 5mg./70Kg. Morphine I.V. (5 subjects)
(Initial 3 post drug observations excluded)

Fitted Common Regression Lines derived by Covariance Analysis :–

I Control Regression $Y = 0.0146 + (0.0235 \pm 0.0018)X$

II Post Drug Regression $Y = 0.0175 + (0.0223 \pm 0.0018)X$

Figure 22

Fitted regression lines (common lines derived by covariance analysis) - CO_2 output related to ventilation before and after 5 mg/70 Kg. morphine (initial three post-drug periods excluded from computations)

I Control $\dot{V}_{CO_2} = .0146 + (.0235 \pm .0018)\ \dot{V}_E$

II Post-drug $\dot{V}_{CO_2} = .0175 + (.0223 \pm .0018)\ \dot{V}_E$

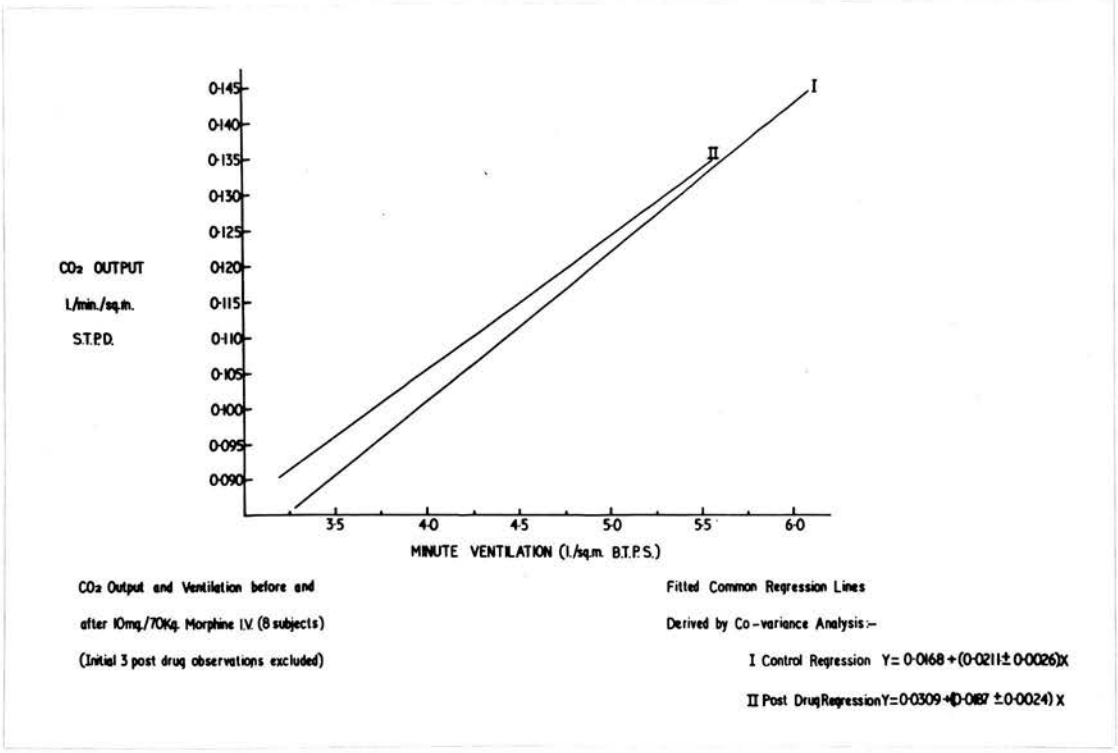
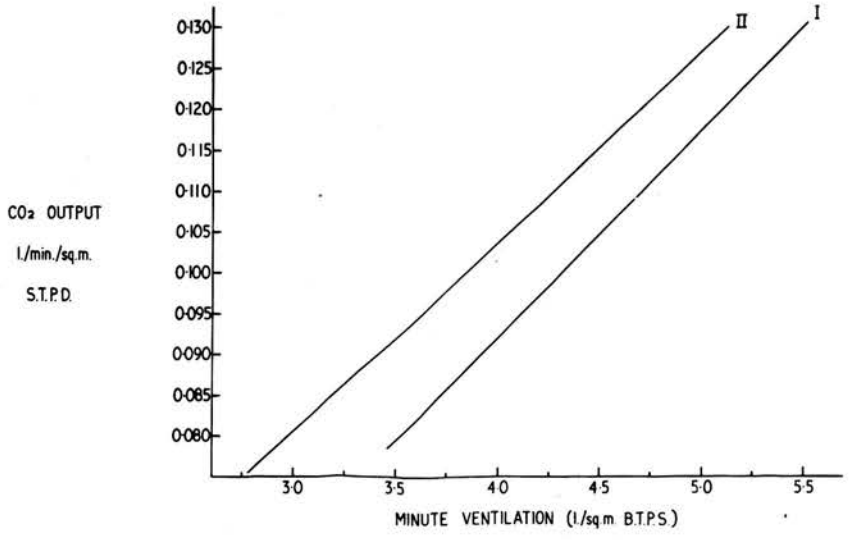


Figure 23

Fitted regression lines (common lines derived by covariance analysis) - CO_2 output related to ventilation before and after 10 mg/70 Kg. morphine (initial three post-drug periods excluded from computations)

$$\text{I} \quad \text{Control } \dot{V}_{CO_2} = .0168 + (.0211 \pm .0026)\,\dot{V}_E$$

$$\text{II} \quad \text{Post-drug } \dot{V}_{CO_2} = .0309 + (.0187 \pm .0024)\,\dot{V}_E$$



CO_2 Output and Ventilation before and after 15mg./70Kg. Morphine I.V. (9 subjects) (Initial 3 post drug observations excluded)

Fitted Common Regression Lines Derived by Co-variance Analysis :-

I Control Regression $Y = -0{\cdot}0088 + (0{\cdot}0235 \pm 0{\cdot}0026)\ X$

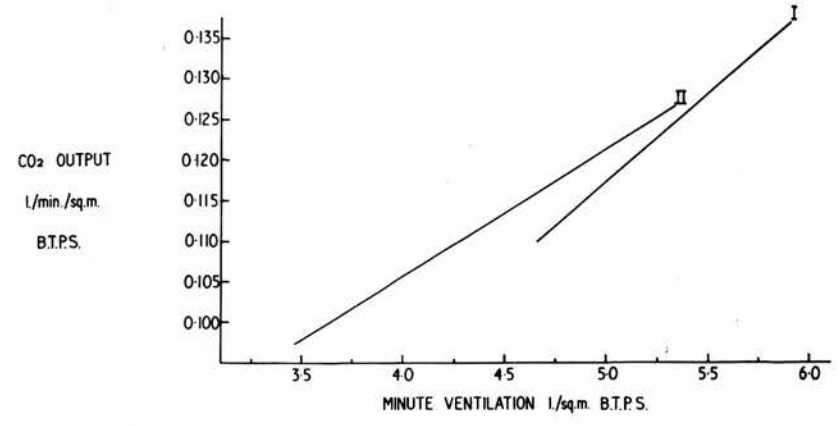
II Post Drug Regression $Y = 0{\cdot}0107 + (0{\cdot}0232 \pm 0{\cdot}0017)\ X$

Figure 24

Fitted regression lines (common lines derived by covariance analysis) - CO_2 output related to ventilation before and after 15 mg/70 Kg. morphine (initial three post-drug periods excluded from computations)

I Control $\dot{V}_{CO_2} = .0088 + (.0235 \pm .0026)\ \dot{V}_E$

II Post-drug $\dot{V}_{CO_2} = .0107 + (.0232 \pm .0017)\ \dot{V}_E$



CO_2 Output and Ventilation before and after 20mg./70 Kg. Morphine I.V. (4 subjects)

(Initial 3 post drug observations excluded)

Fitted Common Regression Lines

Derived by Co-variance Analysis :-

I Control Regression

$Y = 0{\cdot}0081 + (0{\cdot}0218 \pm 0{\cdot}0051)X$

II Post Drug Regression

$Y = 0{\cdot}0435 + (0{\cdot}0156 \pm 0{\cdot}0029)X$

Figure 25

Fitted regression lines (common lines derived by covariance analysis) - CO_2 output related to ventilation before and after 20 mg/70 Kg. morphine (initial three post-drug periods excluded from computations)

$$\text{I} \quad \text{Control } \dot{V}_{CO_2} = .0081 + (.0218 \pm .0051)\ \dot{V}_E$$

$$\text{II} \quad \text{Post-drug } \dot{V}_{CO_2} = .0435 + (.0156 \pm .0029)\ \dot{V}_E$$

The elevation of the 20 mg/70 kg regression line above its own control line is less than the similar elevation of the 15 mg/70 kg post drug line, and only very slightly greater than that relating to the 10 mg/70 kg regression. However, the slope of the post drug line in the 20 mg/70 kg group is appreciably less than that of its control, though not significantly so in the statistical sense. It is likely, therefore, that the 20 mg/70 kg dose has both flattened the curve and displaced it upwards - that is, that its effect in increasing carbon dioxide formation was more marked than that of any of the lesser doses. It will be recalled that a similar effect upon oxygen uptake was suggested.

The effect of morphine upon carbon dioxide output may be summarised as follows. In each treatment group, a significant depression in carbon dioxide output occurred. This change is significantly related to changes in ventilation and, independently to a greater extent numerically, to changes in oxygen uptake. The changes in carbon dioxide output are not significantly related to the dose administered, no doubt, because of this closer dependence upon the changes in measured oxygen uptake - these latter being not significantly related either to the dose administered or to changes in ventilation. Regression analysis shows, further, that the drug affects carbon dioxide output independently of ventilation, presumably by altering the amount of endogenous carbon dioxide formation - an effect which is related to the size of dose administered. During the period covered by these analyses, a dose of 5 mg/70 kg depresses carbon dioxide formation

independent of ventilation and 10, 15 and 20 mg/70 kg, in that order, increase the amount of endogenous carbon dioxide formation.

These effects are, in every respect, analogous with the previously demonstrated effects upon oxygen uptake. They may, therefore, be briefly outlined as follows:

1. A depressant effect upon carbon dioxide output due to a fall in ventilation.

2. A depressant effect upon carbon dioxide output, independent of the effect on ventilation, due to increased carbon dioxide formation, demonstrable only in the 5 mg/70 kg group.

3. A stimulant effect upon carbon dioxide output, independent of an effect on ventilation due to increased carbon dioxide formation, and demonstrable after doses of 10, 15 and 20 mg/70 kg.

Changes in Arterial Carbon Dioxide Tensions and pH after Morphine[1]

Arterial carbon dioxide tensions and pH were measured in 13 normal subjects only. Three control and, usually, 12 post drug samples drawn at consecutive 5 minute intervals were examined. In 2 subjects (G.F. and J.R. in the 10 and 20 mg/70 kg groups respectively) only 7 and 9 post drug samples were examined (Table 17, Figure 26).

Arterial blood samples were examined in 5 of the 6 subjects in the 5 mg/70 kg treatment group, in all 4 subjects in the 20 mg/70 kg group and in only 2 subjects in each of the groups receiving 10 and 15 mg/70 kg morphine. Consequently, for ease of statistical treatment, the four subjects in these two last-named groups have, for some purposes, been considered together as one pooled 10 and 15 mg/70kg group.

An increase in arterial carbon dioxide tension during the post drug period almost invariably occurred (Figure 26, Table 17). One subject only in the 5 mg/70 kg group failed to show such an increase. This increase in P_aCO_2 ranged from less than 1 mm.Hg to 5.3 mm.Hg. The mean increase in all 13 subjects considered together was $2.76 \pm .4866$ with a standard deviation of 1.755 and was highly significant ($P < .001$).

In the 5 mg/70 kg treatment group, 2 subjects showed a significant increase in P_aCO_2, 2 a non-significant increase and, 1 a small non-significant fall. In the remaining subjects the rise in arterial carbon dioxide tension was significant, except for one subject (J.R.) in the

(1) Owing to laboratory mishap some control PO_2 samples were lost and consequently it was decided not to report the data on PO_2 in normal subjects.

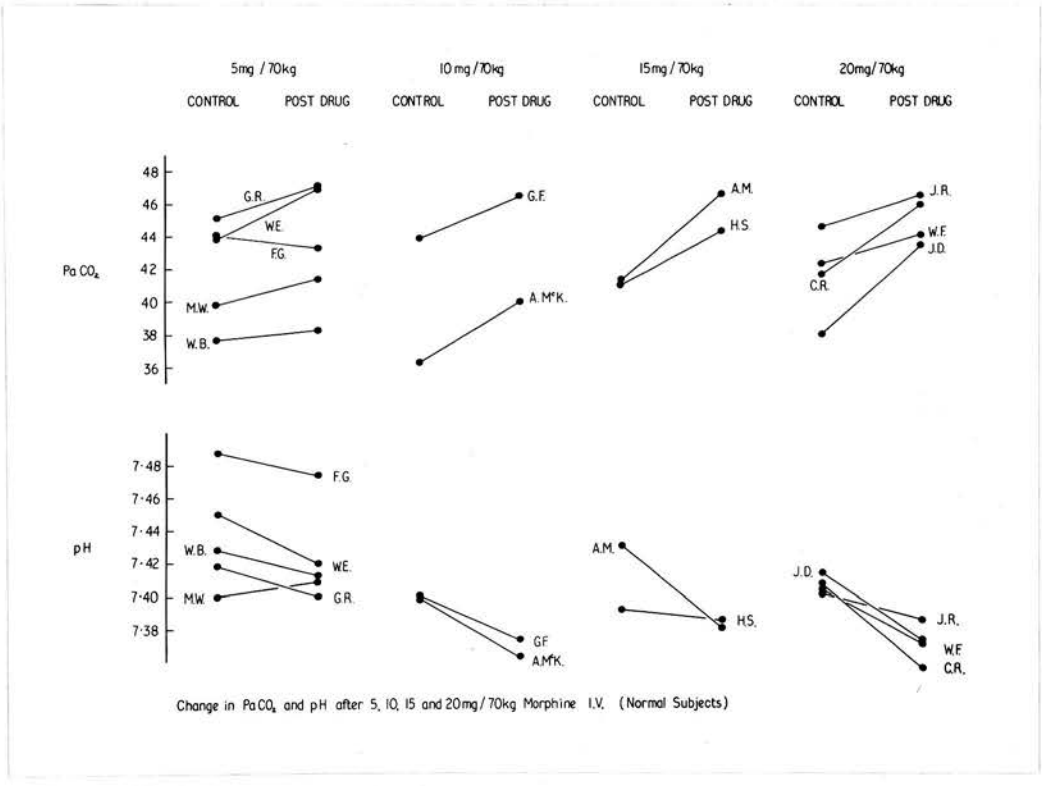


Figure 26

Changes in $PaCO_2$ and arterial pH (13 normal subjects) after 5, 10, 15 and 20 mg/70 Kg. morphine (normal subjects).

20 mg/70 kg group, in whom the increase in P_aCO_2 was short of the .05 level of significance.

The mean increase in the 10 and 15 mg/70 kg combined group and in the 20 mg/70 kg group was, in each case, significant ($.01 > P > .001$ and $.05 > P > .02$ respectively). The mean increase in P_aCO_2 in the 5 mg/70 kg group was not significant ($.2 > P > .1$).

Analysis of variance shows that there is a significant dose effect ($.05 > P > .025$). Detailed testing shows that this is due entirely to the significantly smaller increase in P_aCO_2 in the 5 mg/70 kg group. There is no significant difference between the 10 and 15 mg/70 kg combined group and the 20 mg/70 kg group in regard to the post drug increase in arterial carbon dioxide tension. The mean increase caused by the larger dose is, in fact, slightly less.

The measured values of P_aCO_2 have been used to calculate physiological dead space and alveolar ventilation (Table 18).

Arterial pH almost invariably fell during the post drug period, particularly after the larger doses in excess of 5 mg/70 kg when a significant degree of acidosis developed (Table 17, Fig. 26).

The reasons for the increase in arterial carbon dioxide tension after administration of morphine will now be considered. Intuitively, it might be thought that the depression in ventilation which was induced by all doses used would explain this increase. However, the fractional

changes in P_aCO_2 do not correlate significantly either with changes in total ventilation ($r = -.317$, $n = 13$, $P > .1$ Figure 27) or, with changes in alveolar ventilation ($r = -.350$ $P > .1$). The estimated slopes of the fitted regression lines, while negative, are, neither significant ($P > .2$) :-

$$\text{Fractional changes in } P_aCO_2 = .0451 - (.2073 \pm .1872) \times \text{change in total ventilation}$$

$$= .0457 - (.2203 \pm .1776) \times \text{change in alveolar ventilation}$$

The treatment groups do not show significant slope differences among themselves and the common regression line derived by covariance analysis also has a non-significant slope ($P = .4$) :-

$$\text{Fractional change in } P_aCO_2 = .0877 + (.1838 \pm .2070) \times \text{fractional change in total ventilation}$$

The standard deviation from regression is .0360

Although these statistics suggest that a larger number of observations might have demonstrated a significant relationship, clearly, the fall in ventilation cannot be the principal cause of the recorded increase in arterial carbon dioxide tension.

By contrast, for all observations considered together, fractional changes in P_aCO_2 correlate significantly with fractional changes in oxygen uptake ($r = .596$ $.05 > P > .02$). The fitted regression line (figure 28) has the equation :-

$$\text{Fractional change in } P_aCO_2 = .0826 + (.9400 \pm .3820) \times \text{fractional change in oxygen uptake}$$

The slope is significant and the standard deviation from regression is .0374.

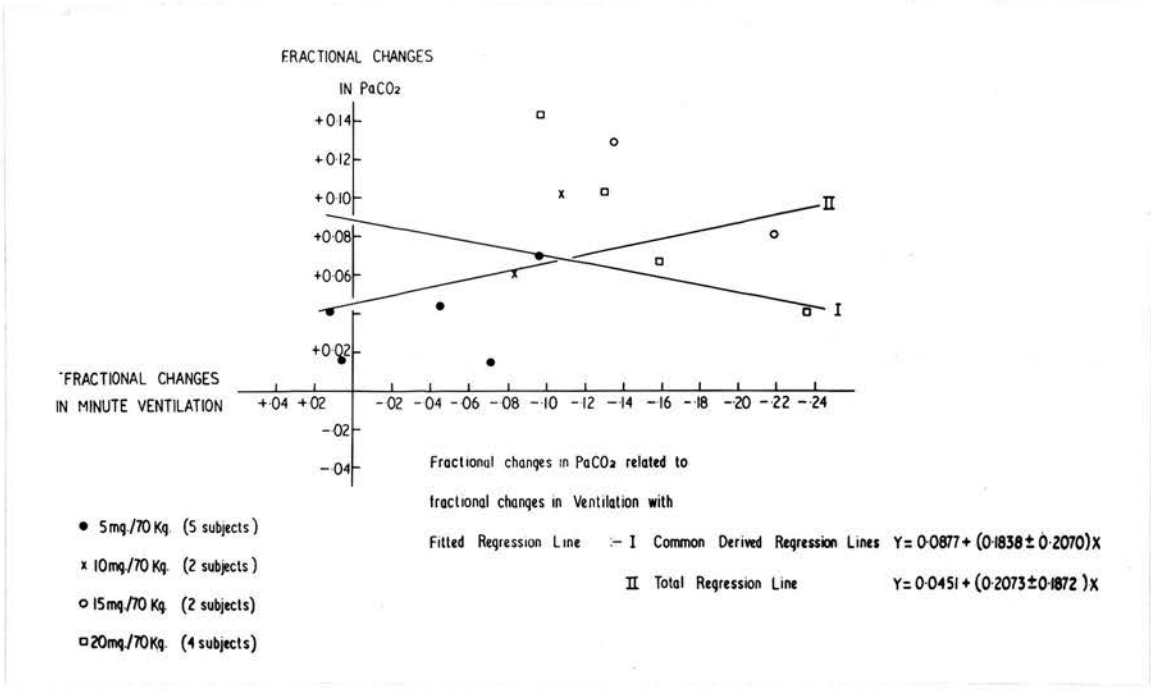


Figure 27

Fitted regression line - Fractional changes in Pa CO_2 related to fractional changes in ventilation after morphine (normal subjects).

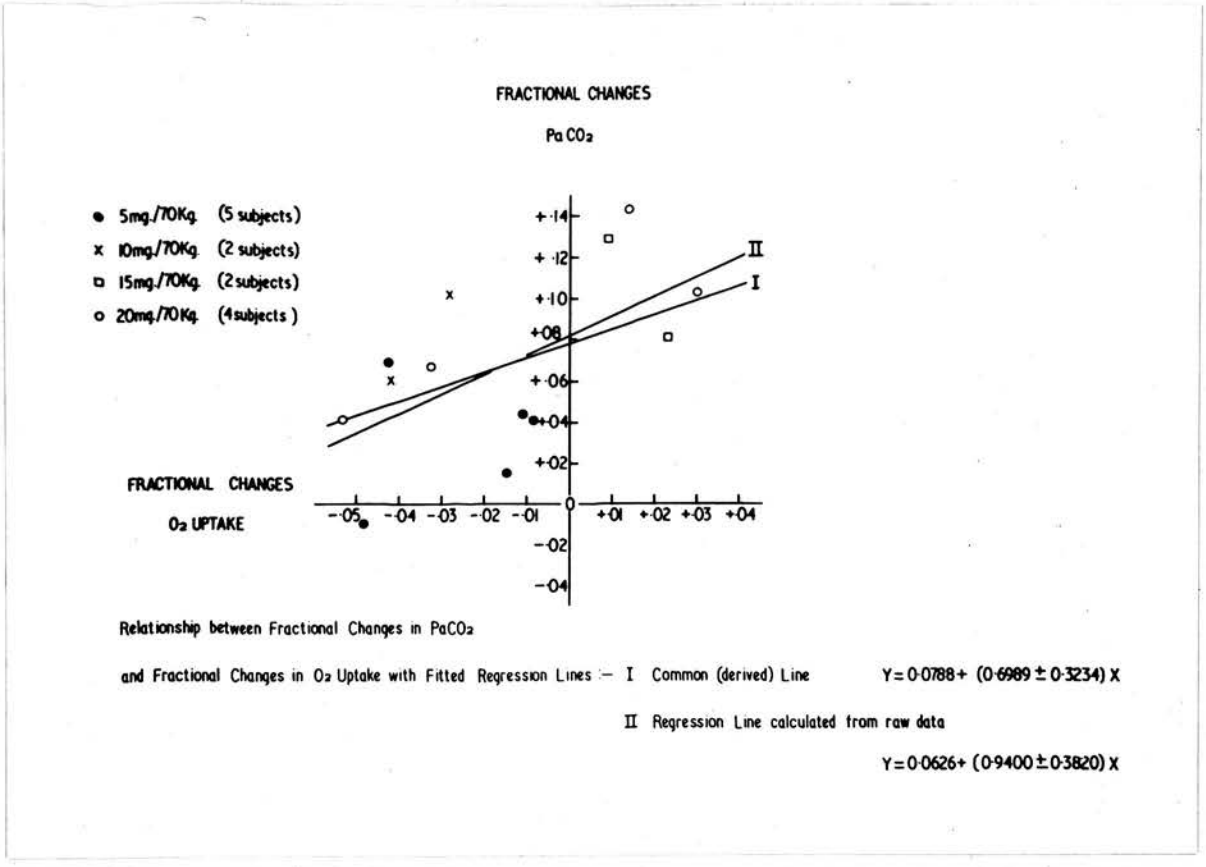


Figure 28

Fitted regression line - Fractional changes in $PaCO_2$ related to fractional changes in O_2 uptake after morphine (normal subjects).

The common regression derived by covariance analysis probably yields a more valid estimate of slope than the foregoing even though the loss of 2 degrees of freedom makes this not quite significant at .05 level :-

$$\text{Fractional change in } PaCO_2 = .0718 + (.6989 \pm .3234) \times \text{fractional changes in oxygen uptake}$$

with a standard deviation from regression of .0305.

Presumably this estimate incorporates a negative effect attributable to compensatory influences upon minute ventilation, produced by changes in oxygen uptake. This latter effect would explain, in part, why changes in ventilation do not correlate significantly with changes in P_aCO_2.

These results indicate that, after morphine, the rise in arterial carbon dioxide tension is caused, not mainly by the fall in ventilation, but to a greater extent, by the changes in oxygen uptake.

The changes in arterial carbon dioxide tension have been further examined by the use of regression analysis, in a manner similar to that used for oxygen uptake and carbon dioxide output. The regression relationship chosen has been that of arterial P_{CO_2} on alveolar ventilation. It is generally accepted that P_aCO_2 is more closely related to alveolar than to total ventilation, and the observations in the present study confirm this. The respective regressions derived by covariance analysis and relating to the control period are as follows :-

$$PaCO_2 = 48.656 - (1.485 \pm .809)\ \dot{V}_E \qquad (1)$$

$$PaCO_2 = 47.89 - (1.938 \pm .719)\ \dot{V}_A \qquad (2)$$

with standard deviations from regression of .9913 and .8731 respectively and 21 degrees of freedom. Three paired control observations from each subject have been used for computing these statistics. Equation (1) has a non-significant slope ($.1 > P > .05$) and has been derived from data contributed by all four treatment groups. Equation (2) has a significant slope ($.02 > P > .01$) but, in computing the statistics the 2 subjects of the 10 mg/70 kg group have been excluded because of significant slope differences from the rest of the population ($.05 > P > .025$). From the statistics in Table 19, it is evident that only about 25% of variation in $PaCO_2$ is to be attributed to alveolar ventilation.

Control and post drug regressions have been compared, in the usual way, for differences in slope and elevation. Owing to the limited number of observations it was not possible to make a useful estimate of control slope for each treatment group separately. Consequently, the slope of equation (2) has been assumed for eachof the treatment groups individually, except the 10 mg/70 kg group which, for the reason given above, could not be incorporated in this estimate. For computing the adjusted means, the actual observed mean in each treatment group has been used. The actual computed control regression of the 10 mg/70 kg has been used even though this is not a very satisfactory estimate and is based on a very limited number of observations. In calculating the post drug regressions, extreme values during the initial period of hyperpnoea have, where present, been excluded because experience has shown that this results in more satisfactory estimates.

The results of these analyses are set out in Table 19 and the fitted regression lines in Fig. 29. The 5 mg/70 kg post drug slope is significant ($.01 > P > .001$). The 10, 15 and 20 mg/70 kg post drug slopes are not ($P > .1$, $> .05$ and $> .1$ respectively). Comparison of these slopes by covariance analysis shows no evidence of significant differences among them. The common post drug slope derived by pooling the data from all treatment groups is highly significant ($P < .001$). Thus, it would appear that both before and after drug administration P_aCO_2 is significantly related to alveolar ventilation. However, the non-significant slopes in the 10, 15 and 20 mg/70 kg groups cannot be due to any limitation in the available degrees of freedom and require explanation. The likely explanation is that doses of morphine greater than 5 mg/70 kg have affected ventilation and P_aCO_2, to some extent, independently even though the linear relationship between the two is readily apparent from the fitted regression lines in Figure 29.

That this is the probable explanation is suggested by a consideration of the differences in elevation of the control and post drug regression lines.

Although the post drug slopes are slightly larger than the common control slope, these differences are not significant, and, in consequence, the adjusted means may usefully be compared (Table 19). The 5, 15 and 20 mg/70 kg adjusted means are significantly larger than the control: the adjusted mean of the 10 mg/70 kg post drug regression line is also larger than its control, but not significantly so, probably because of the rather inadequate estimate of control regression available. From Table 19, it would appear

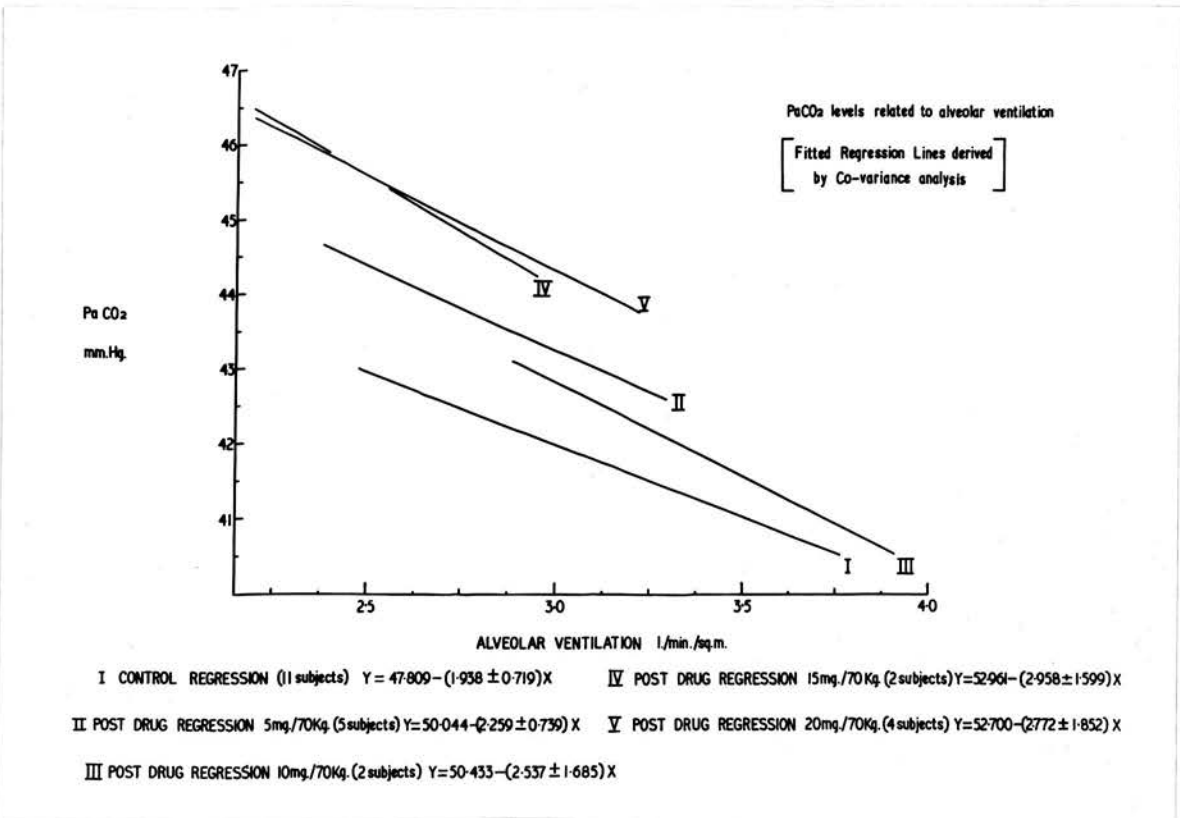


Figure 29

Fitted regression lines - $PaCO_2$ related to alveolar ventilation ($\dot{V}_A$) - Control and post-drug periods for normal subjects computed as described in the text.

that the elevation of post drug regression is, to some extent, related to dose, increasing from 5 to 15 mg/70 kg and, then, levelling off. The elevation of the 5 mg/70 kg post drug regression line is quite small - a little less than 1 mm.Hg - but is nevertheless very significant.

These findings indicate clearly that morphine produces independent effects also upon alveolar ventilation and arterial carbon dioxide tension, and therefore, confirm that the increase in P_aCO_2 cannot be due entirely to the decline in alveolar ventilation. That this decline in ventilation plays a significant role is suggested by intuition and indicated by the significant slopes of the regression lines: that this decline is not the principal cause of the increase in P_aCO_2 after administration of morphine, particularly after doses in excess of 5 mg/70 kg, is shown by the non-significant slope in these treatment groups post drug and the dose related increase in elevation of the post drug regression line in all treatment groups. The demonstration earlier that fractional changes in P_aCO_2 are significantly correlated not with changes in ventilation but with changes in oxygen uptake: and that morphine causes an increase in oxygen consumption and endogenous carbon dioxide formation independent of its effect on ventilation: - these indicate very strongly and almost conclusively that the increase in arterial carbon dioxide tension is caused mainly by these stimulant effects of the drug upon metabolism and the consequent increase in endogenous carbon dioxide formation which this entails.

These regressions emphasise further what a relatively slight effect upon metabolism is produced by a dose of 5 mg/70 kg.

It is to be noted that the drug apparently caused an increase in slope which, although not statistically significant, might well represent a real drug effect.

The effects of morphine on arterial carbon dioxide tension may, therefore, be summarised as follows. Each dose administered caused an increase in P_aCO_2 which was non-significant in the 5 mg/70 kg group and significant in the other groups. By the rather more sensitive method of regression analysis it was shown that even the very small increase in the 5 mg/70 kg group was statistically significant. Although the decline in alveolar ventilation does contribute to the increase in arterial carbon dioxide tension, a more important cause of the latter is the stimulat effect of the drug upon metabolism and the consequent increase in endogenous CO_2 formation.

Effect of Morphine on the Sensitivity of the Respiratory Centre to Arterial Levels of PCO_2

The increase in arterial or alveolar carbon dioxide tension which has long been known to occur after morphine in the presence of depression of ventilation has been generally regarded as an indication that the sensitivity of the respiratory centre is depressed by the drug. This is no doubt correct in the above sense. However, sensitivity defined as the variation in ventilation as a function of the variation in $PaCO_2$ - $\Delta\dot{V}/\Delta PaCO_2$ - has never been shown to be affected by morphine.

The observation that carbon dioxide formation and ventilation are, in significant degree, independently influenced by the drug, provides an opportunity for studying $\dot{V}_A/PaCO_2$ relationships over a range of values never before studied. An attempt has, therefore, been made to find out whether any evidence can be obtained from these relationships of any change in sensitivity to carbon dioxide as above defined.

Alveolar ventilation/$PaCO_2$ regressions were computed in the usual way by covariance analysis for the control period. As in the previous section, the slope contributed by the 2 subjects in the 10 mg/70 kg group is a serious source of heterogeneity and has been excluded from the estimate of common control slope. The derived common slope is significant ($.02 > P > .01$) and negative:-

$$\dot{V}_A = 8.6807 - (.1325 \pm .0492) \times PaCO_2$$

The assumption is made that this reciprocal relationship between $\dot{V}_A$ and P_aCO_2 incorporates a component, which cannot be measured directly, attributable to the sensitivity of the respiratory centre to changes in P_aCO_2.

Post drug regressions have been computed in the same way (Table 20) The post drug slopes are, in each treatment group, flatter than the control slope and all are, of course, negative. However, the difference from the control slope is significant only in the case of the 20 mg/70 kg slope ($.05 > P > .02$). The 5 and 15 mg/70 kg post drug slopes, although appreciably smaller than the common control slope are neither significantly different in the statistical sense from this. The 10 mg/70 kg post drug slope is, also, significantly less than its own rather inadequate estimate of control slope ($.05 > P > .025$). The tests of adjusted means shows that the elevations of the 5 and 15 mg/70 kg regression lines are significantly depressed - this merely confirms what is already known, namely, that after morphine larger P_aCO_2 levels are found for a given level of ventilation than would be recorded prior to administration of the drug. In that sense, the CO_2 sensitivity has been diminished.

The quotient $\Delta\dot{V}_A/\Delta P_aCO_2$ cannot be measured directly but certain assumptions are permissible. First, it is to be assumed that, under all conditions, the respiratory centre is sensitive to changes in P_aCO_2. Second, it may validly be assumed that this sensitivity, as expressed by the quotient $\Delta\dot{V}_A/\Delta P_aCO_2$ is incorporated in the above estimate of slope.

It is apparent also that this negative slope, invariably present over the range of values studied would become steeper as the dependence of $P_a CO_2$ upon ventilation becomes more marked, for example, when ventilation is, for any reason, varying over wide limits. In such a situation the $\dot{V}_A / P_a CO_2$ regression is hardly if at all influenced by the sensitivity of the respiratory centre to carbon dioxide. Under more stable conditions this reciprocal relationship between ventilation and $P_a CO_2$ as embodied in the negative regression slope still holds, but, it may be assumed that the ideal quotient $\Delta \dot{V}_A / \Delta P_a CO_2$ then represents a significant part of the slope estimate and is responsible for the tendency of the slope to flatten under resting quiet conditions.

It follows, therefore, that if no factor other than the quotient $\Delta \dot{V}_A / \Delta P_a CO_2$ had altered, then, an "increased CO_2 sensitivity" should result in flattening or reversal of slope while a "decreased CO_2 sensitivity" should increase the negative slope.

It will be observed from the statistics in Table 20 that all doses used decreased the estimated slope of the $\dot{V}_A / P_a CO_2$ regression, that is, there was an apparent increase in sensitivity to $P_a CO_2$; or put in another form, morphine appears to improve efficiency of homeostasis at the selected alteredrange of $\dot{V}_A$ and $P_a CO_2$. This is, however, probably not true.

It has been shown earlier that ventilation and carbon dioxide formation, and consequently $P_a CO_2$ levels are independently influenced by morphine -

the former being depressed and the latter increased. This circumstance would itself tend to flatten the slope of $\dot{V}_A / P_a CO_2$ regression. It seems likely that this is the cause of the major part of the slope decrease which occurred. This interpretation is entirely consistent with the finding that the decrease in slope appears to some extent to be dose related.

These results do not therefore provide any support for the view that morphine depresses respiration by depressing the sensitivity of the respiratory centre to carbon dioxide. Can it be stated, however, that carbon dioxide sensitivity is unaltered by morphine ? It is conceivable that the metabolic effects are so marked that slope effects which might otherwise have appeared have been submerged. This, however, seems unlikely. If $P_a CO_2$ increased because of increased CO_2 formation and $\dot{V}_A$ fell because of respiratory depression (through whatever mechanism), then, the negative slope of $\dot{V}_A / P_a CO_2$ regression would clearly have become steeper in the presence of coincidental depression of sensitivity.

It seems most likely, therefore, that sensitivity as defined by the quotient $\Delta \dot{V}_A / \Delta P_a CO_2$ is neither depressed nor enhanced by the doses of morphine administered. On the contrary, the regression statistics indicate that normal homeostasis is achieved, in all treatment groups studied, in relation to the selected new levels of alveolar ventilation and arterial CO_2 tension.

These conclusions, while fully supported by the data presented, are offered with certain reservations. It is manifestly desirable that an acceptable control slope should be separately computed for each treatment

group before it can be accepted as proven that the changes in slope are due to the drug. It seems likely from the estimates of statistical parameters presented in Table 20 that the conclusions are not likely to be materially challenged when such control slopes are available.

EFFECTS OF MORPHINE IN PATIENTS SUFFERING FROM LEFT VENTRICULAR FAILURE

Six patients suffering from left ventricular failure were studied by means of a protocol identical with that used in the normal subjects (Table 1, Figure 1). Because of their clinical state they were studied sitting propped up in their beds. Morphine 15 mg/70 kg was administered to these patients because this is a dose very commonly used therapeutically in this condition.

Personal Particulars and Control Observations

Clinical Details

Case summaries in respect to the six patients studied are given at the end of this section.

When studied, these patients showed signs and symptoms of congestive heart failure, which was believed to be of the left ventricular type, namely, raised jugular venous pressure, orthopnoea and basal crepitations. In one subject (R. McI.) symptoms were rather slight, another was only moderately distressed and, in the remaining subjects, symptoms were severe or very severe. All patients were fully assessed clinically as to their fitness for the study and all consented to the invitation to participate.

Left ventricular failure was due to hypertensive disease in 3 subjects (D. McA., R. McI., and A. G.) and was secondary to ischaemic heart disease in 3 (A. O., A. M., and E. S.).

Age

Apart from one subject aged 30 years, with hypertension, patients were aged 60 years or over. The mean age in the group of 57.33 is, of course, greater than that of the normal subjects. This age difference is significant whether or not this young patient is excluded from consideration ($.05 > P > .02$). The mean age of the group is also greater though not significantly so than the group of normal subjects in the 15 mg/70 kg group (Table 22).

Control Observations

Mean minute ventilation and respiratory rate during the control period in patients with left ventricular failure were significantly larger than in normal subjects (Table 22). The variance for ventilation in this group is also significantly larger ($P < .001$), an indication mainly of the important differences among the patients in clinical severity of signs and symptoms.

Variability of the control minute ventilation, expressed as the ratio $\frac{\text{Standard Deviation}}{\text{Mean}}$, is rather larger though not significantly so at the .05 level, in the patients with left ventricular failure than in the normal group treated with the same dose of morphine ($.1 > P > .05$). There is no significant difference in variability of control ventilation between this and any other group of normal subjects. The mean variability in the control oxygen uptake of approximately 3% suggests a relatively stable metabolic state and is not significantly different from that of any group of normal subjects.

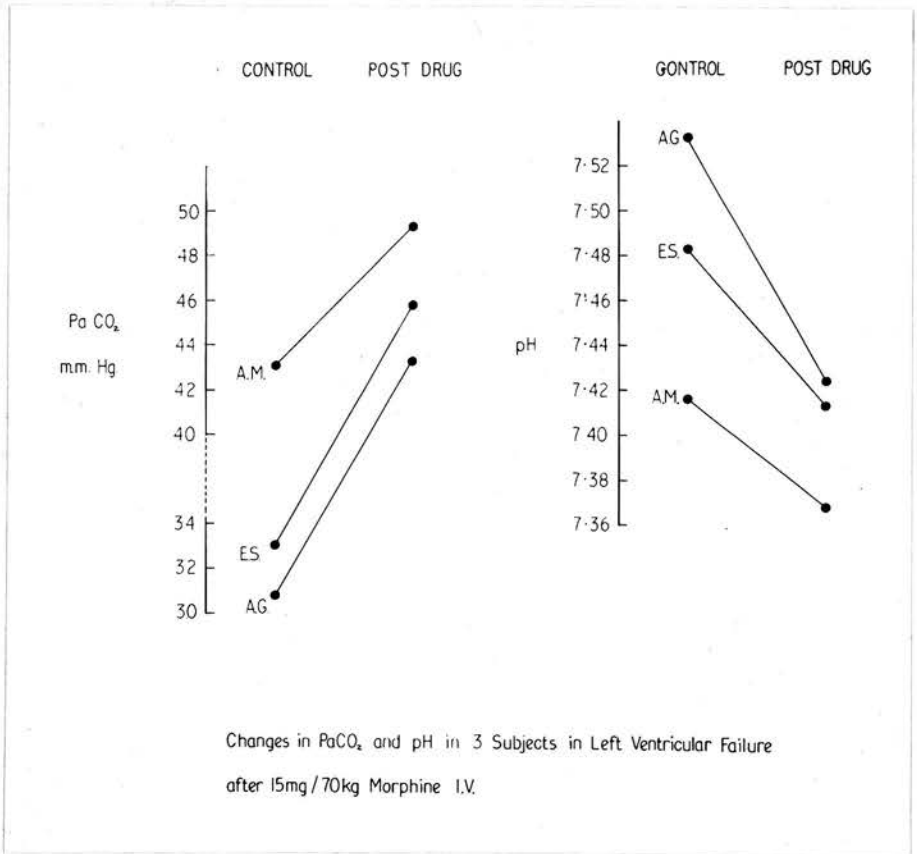
Thus, despite their dyspnoea, patients with left ventricular failure were metabolically stable at the time of the study, while some degree of respiratory instability was present.

Mean tidal volume was somewhat lower in the patients with left ventricular failure but this difference is not signficant ($P > .3$).

The mean control oxygen consumption is slightly larger in the group of patients with left ventricular failure than the normal subjects, a non-significant difference ($P > .6$). Having regard to the significantly larger minute ventilation in the former group, the observed difference in oxygen uptake of 3.3 ml/min is rather unimpressive.

Despite the larger minute ventilation and oxygen uptake, the carbon dioxide output per minute in the group was somewhat less than that of the normal subjects, a non-significant difference.

Arterial gas tensions were estimated in three patients only. One subject was moderately hypoxaemic (P_{O_2} = 69.33 mm.Hg), another was slightly so (P_{O_2} = 82.33), and in the third P_{O_2} was normal (96.67 mm.Hg). P_aCO_2 was low in 2 patients (33 and 30.83 mm.Hg) and within normal limits in the third (43.17). pH values were on the alkaline side of normal. Thus the two severely dyspnoeic patients had normal or low normal P_{O_2}, low P_aCO_2 and alkaline pH. (Table 23, figure 30).



Changes in $PaCO_2$ and pH in 3 Subjects in Left Ventricular Failure after 15mg / 70kg Morphine I.V.

Figure 30

Changes in $PaCO_2$ and arterial pH after 15 mg/70 Kg. morphine. (patients with left ventricular failure).

Effects on Respiration

(Tables 24, 25, Figure 31)

Of the 6 patients studied, 5 experienced a significant fall in minute ventilation. In the sixth (A.O.) depression is just short of significance at .05 level, no doubt, because of the fairly marked initial post drug hyperpnoea which occurred. If this period of hyperpnoea is excluded from consideration, the subsequent depression is significant ($.05 > P > .02$). The mean depression in minute ventilation in the group is significant ($.01 > P > .001$).

The respiratory frequency fell significantly in 5 patients. In the sixth (A.G.) there was a very small and non-significant increase. The mean depression in respiratory frequency in the group is significant, ($.05 > P > .02$).

The fractional depression in minute ventilation in the group is appreciably larger than that which occurred in normal subjects treated with the same dose of morphine (Table 25), but this difference is only just significant ($P = .05$, nearly). The fractional depression in respiratory frequency is also larger than in the normal group given 15 mg/70 kg but not significantly so ($P > .3$).

The changes in tidal volume are more variable. In 4 patients, there was a significant change - in 2 this increased and in 2 there was a decline. In the remaining 2 subjects, there was non-significant fall in tidal volume. The mean depression in tidal volume of approximately 5% is not significant ($P > .5$). This also is larger than the depression recorded in the normal group, but the difference is not significant ($P = .7$).

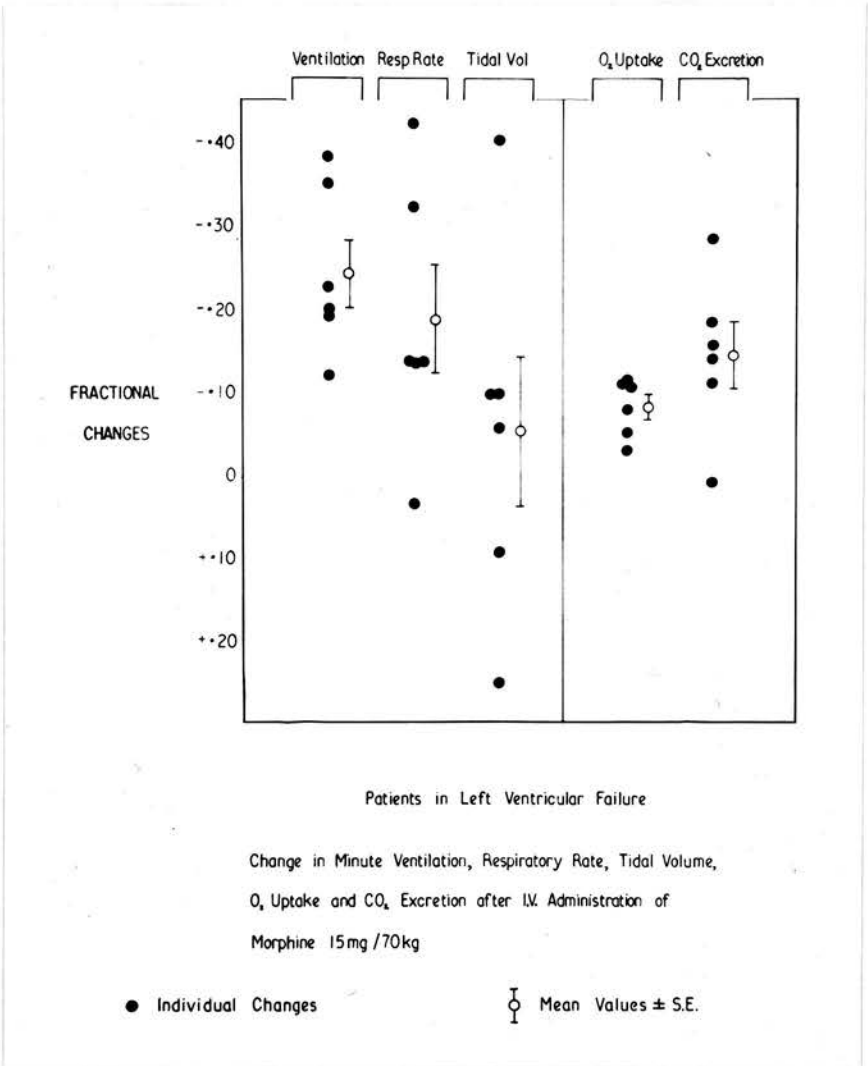


Figure 31

Changes in minute ventilation, respiratory frequency, tidal volume, O_2 uptake and CO_2 output after 15 mg/70 Kg. morphine (patients with left ventricular failure).

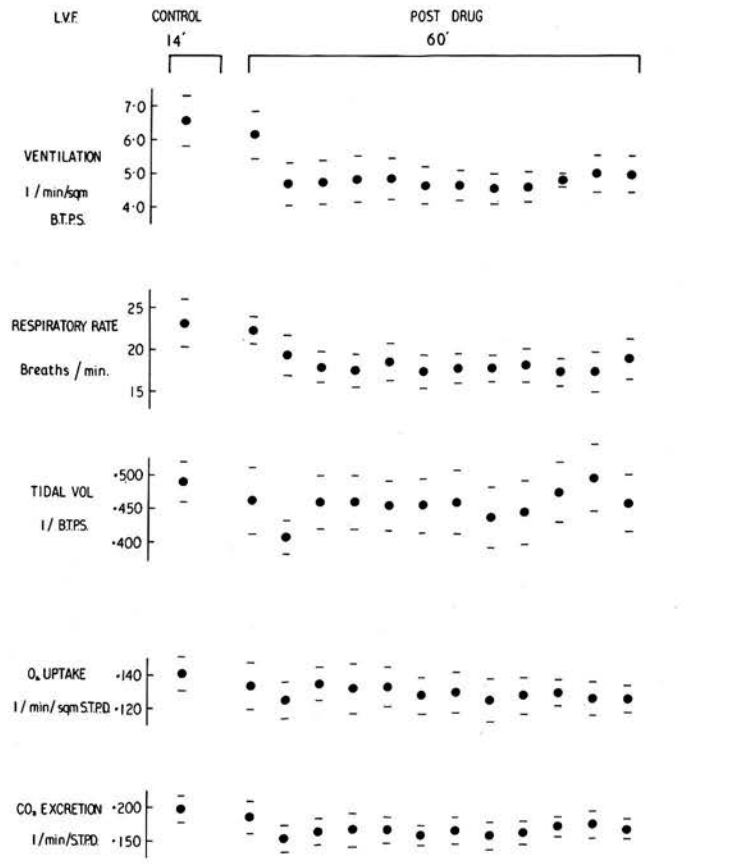
The changes in respiration, in relation to time, are shown in Figure 32. Mean ventilation, respiratory frequency and tidal volume fell during the first post drug period and tended to remain depressed for the remainder of the post drug period. The plotted changes are remarkably similar to those recorded in the normal group treated with 15 mg/70 kg morphine (figures 2, 9, 11). It is to be noted that, although the minute ventilation fell very considerably, the post drug values are still appreciably larger than those of the normal group.

Post Drug Hyperpnoea in Patients with Left Ventricular Failure (Table 12, figure 33)

In all patients, an increase in minute ventilation which, in 3 subjects, was very marked, occurred furing the first minute following drug administration (Fig. 33). The mean fractional increase of approximately 25%[1] is, however, marginally short of the .05 level of significance, no doubt because of the marked variability of the response (Table 12). The normal treatment groups in which post drug hyperpnoea was marked also showed,it will be remembered, similarly marked variability of response.

During the subsequent 3 minutes, two patients continued to show some increase in ventilation as compared with the control period, albeit in diminishing degree. In the remaining patients overbreathing ended during the second minute following drug administration.

(1) One subject (D. McA.) excluded from the calculations because of a very short break in the spirometer record.



Minute Ventilation, Respiratory Rate, Tidal Volume, O_2 Uptake and CO_2 Excretion before and after 15 mg / 70kg Morphine I V to patients in Left Ventricular Failure

● Mean Values ± S.E. Control: Mean Values during 3 successive 4min periods immediately prior to injection.

Post Drug: Mean Values during 12 successive 4min periods following injection.

Figure 32

Changes in minute ventilation, respiratory frequency, tidal volume, O_2 uptake and CO_2 output in relation to time, after 15 mg/70 Kg. morphine (patients with left ventricular failure).

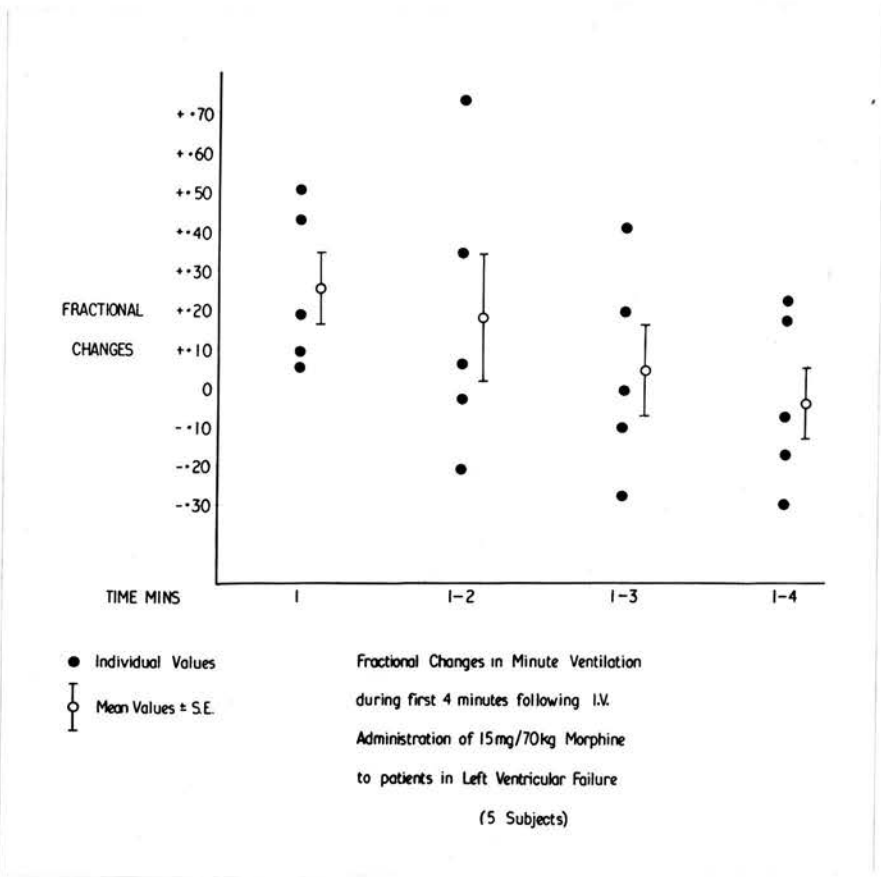


Figure 33

Fractional changes in ventilation during first 4 minutes after injection of 15 mg/70 Kg. (patients with left ventricular failure)

This immediate increase in ventilation in the group of patients suffering from left ventricular failure is to be contrasted with the behaviour of normal subjects given the same dose of morphine. In this group, as pointed out the previous section,(2) an initial hyperpnoea, though sometimes recorded, was very uncommon and never as marked.

In two subjects (A.O. and D.McA.), oxygen uptake increased during the first post drug period.

Changes in Oxygen Uptake
(Tables 21, 24 and 25)

Although the control ventilation is considerably greater in patients with left ventricular failure than in the normal group (Table 22), the difference in oxygen uptake is very slight and, in the statistical sense, non-significant. It will be noted from Figure 34 that the plotted mean values for ventilation and oxygen uptake in the group nearly all lie below the normal control $\dot{V}_{O_2}/\dot{V}_E$ regression line. That this difference in oxygen uptake is highly significant can be shown, in the usual way, by regression analysis. In Figure 35 are shown the fitted $\dot{V}_{O_2}/\dot{V}_E$ regression lines derived by covariance analysis. The slopes do not differ significantly but comparison of the adjusted means shows that the elevation of the control regression of the left ventricular group is significantly less than that of the normal control regression ($P < .001$). Thus, patients suffering from left ventricular failure had a significantly lower oxygen uptake than normal subjects for the level of ventilation achieved.

(2) Page 75

Over the 60 minute period following drug administration, oxygen consumption fell in all 6 patients, but this was significant only in 2 patients (Table 24, figure 33). The depression in oxygen uptake varied from 4 - 16 mls per minute. The mean fractional change in the group of approximately 8% was very significant ($.01 > P > .001$). This depression in oxygen uptake is appreciably and significantly greater than that which occurred in the group of normal subjects to whom the same dose of morphine was administered ($.02 > P > .01$). Even so, the change in oxygen uptake is proportionally considerably less than the change in ventilation - a discordance which, as previously noted, exists also in the normal treatment groups (Table 25, figure 31).

The mean changes in oxygen uptake in the group in relation to time illustrated in Figure 32 show that oxygen uptake fell early in the post drug period and remained depressed throughout. The sharp initial fall in oxygen uptake noted in the normal group (figure 12) is not apparent, presumably because of the initial increase in ventilation which occurred in all subjects with left ventricular failure.

The changes in oxygen uptake have been further considered, as in the normal subjects, by the methods of regression analysis. The regression chosen is, as in the normal groups, that of oxygen uptake on ventilation. The common control regression computed by covariance analysis showed evidence of significant slope heterogeneity which could be attributed to the data contributed by one subject (A.G.). After exclusion of this subject from

thegroup an entirely satisfactory estimate of control regression was obtained. In estimating the post drug regression, the initial 3 periods have, for the reasons previously given, been excluded. The estimate of post drug regression so obtained shows no evidence of significant slope differences among patients. It was considered preferable not to exclude from the computation of post drug regression the patient dropped from the control estimate.

The results are shown in Table 26 and the fitted regression lines in Figure 35. Both slopes are significant, the post drug slope being slightly greater than the control but not significantly so. It is evident from Figure 35 that the elevation of the post drug regression line is considerably greater than that of the control and the test of adjusted means confirms that this difference in elevation is highly significant ($P < .001$). Thus in patients suffering from left ventricular failure, also, morphine increases oxygen uptake independent of its effect on ventilation. In the group of patients with left ventricular failure, the increased elevation of the post drug regression line ($.0212 \pm .0024$), as compared with its control, is greater than the corresponding change in the 15 mg/70 kg normal group ($.0130 \pm .0017$), a difference which is without doubt significant. It will be noted also that the elevation of the post drug regression line is still appreciably less than that of the control normal line and also of the post drug regression line of the normal group treated with 15 mg/70 kg morphine.

Thus, patients in left ventricular failure after treatment with morphine continued to show a rather large respiratory minute volume and an appreciably lower oxygen uptake than would be expected from the level of ventilation.

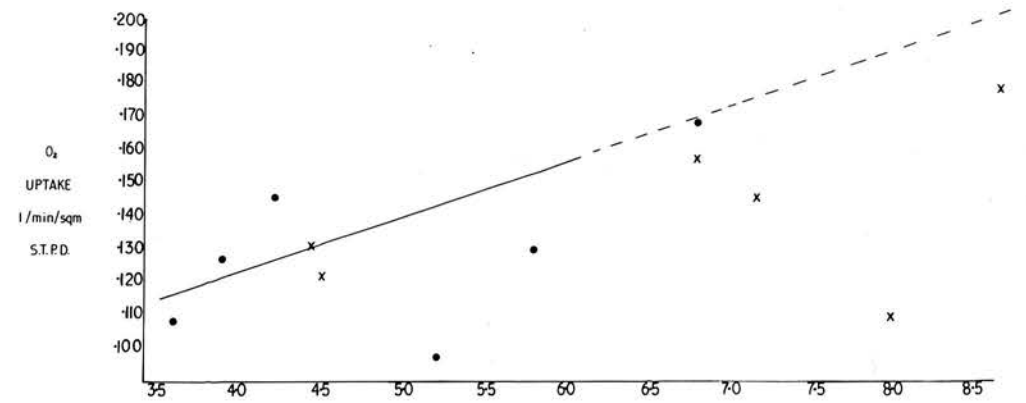


Figure 34

Patients with left ventricular failure - control paired values for O_2 uptake and ventilation plotted in relation to control regression.

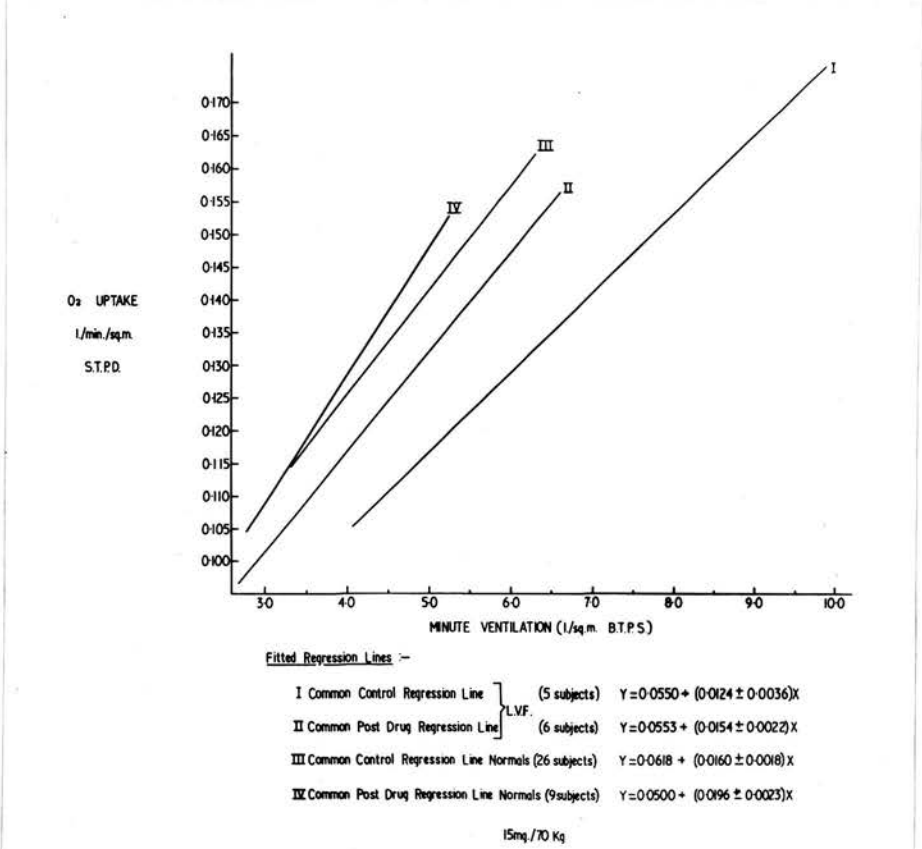


Figure 35

Patients with left ventricular failure: Fitted regression lines - O_2 uptake related to ventilation - control and post-drug regressions compared with regression lines for normal subjects (all regressions derived by covariance analysis).

Changes in Carbon Dioxide Output (Tables 21, 24)

Carbon dioxide output fell in all subjects except one (A.O.) in whom the mean post drug value was almost identical with the control. The depression in carbon dioxide output was significant in 4 patients and non-significant in the fifth. The mean depression in the group was significant ($.02 > P > .01$). The fractional depression in carbon dioxide output is larger than that of oxygen consumption but less than the change in ventilation. The depression in carbon dioxide output is larger, though not significantly so, than that which occurred in the normal group treated with 15 mg/70 kg ($P = .1$) (Tables 21, 24, 25, figure 31).

The changes in carbon dioxide output in relation to time are shown in figure 32. Carbon dioxide excretion fell early in the post drug period and remained depressed thereafter.

As in the normal group, the changes in carbon dioxide output have been studied by the use of regression analysis. Comparison between the control and post drug $\dot{V}_{CO_2}/\dot{V}_E$ regressions makes it possible to separate the effects upon carbon dioxide output attributable to changes in ventilation and those due to other causes. The regression statistics are as follows: -

	r	Degrees of Freedom	S_{yx}	$\bar{Y}$	a + (b ± S.E.)	$\bar{X}$	Control - post drug adjusted mean
Control Regression	.911	23	.0022	.1157	.0128 + (.0156 ± .0015)	6.609	.0157 ± .0019 ****
Post Drug Regression	.939	47	.0040	.0985	.0101 + (.0185 ± .0012)	4.779	

Both slopes are significant and neither estimate shows evidence of significant heterogeneity. The post drug slope is slightly larger, but not significantly so, than the control slope. The post drug adjusted mean is significantly larger than that of the control. The degree of elevation observed (.0157 $\pm$ .0019) is somewhat greater than the elevation of the post drug normal 15 mg/70 kg regression above its own control (.0106 $\pm$ .0011), a difference which is without doubt significant.

Thus in patients with left ventricular failure also the fall in carbon dioxide output after morphine is greater than can be accounted for by the depression in minute ventilation. In these subjects, it is to be presumed that increased carbon dioxide formation consequent upon the increased oxygen uptake is responsible for a significant portion of the change in CO_2 output.

Effect on Arterial Blood Gas Tensions

It was possible to measure arterial blood gas tensions in 3 patients only. Two subjects were hypoxaemic before drug administration while arterial oxygen tension in the third was normal. $P_a CO_2$ was low in 2 and normal in 1 patient. pH was normal in 1 and on the alkaline side of normal in 2 patients (Table 23, figure 30).

After administration of morphine, there was a marked and significant decline in arterial oxygen tension in 2 patients, as measured over the 60 minute post drug period. In the third, mean P_{O_2} measured over the same period was identical with the control value.

Arterial carbon dioxide tension rose significantly in all 3 subjects. The increase was particularly marked in the 2 patients with moderate (A.G.) and severe (E.S.) dyspnoea associated with low control values of P_aCO_2. In these two patients, P_aCO_2 entered the normal range after administration of morphine. The third subject became definitely hypercapnic during the post drug period.

Arterial pH fell significantly in all three patients. In one subject (A.M.) pH fell to acidotic levels in association, as noted above, with a degree of hypercapnia: in the other 2 patients arterial pH remained on the alkaline side of normal after drug administration.

An attempt has been made as in the normal subjects, by the use of $P_aCO_2/\dot{V}_A$ regressions, (v - Table 18), to find out whether the increase in arterial carbon dioxide tensions after morphine can be explained entirely by the fall in ventilation. Owing to the limited number of observations these regressions have been rather difficult to handle. The regression statistics are set out below:-

	r	Degrees of Freedom	S_{yx}	$\bar{Y}$	a + (b ± S.E.)	$\bar{X}$	Control - post drug adjusted mean ± S.E.
Control	.811	5	.4778	35.667	42.076 - (1.645* ± .531)	3.89	-6.608 ± 3.309
Post drug	.296	24	3.450	47.018	58.657 - (4.622(1) ± 3.107)	2.518	.1 > P > .05

(1) difference from control slope is not significant (.4 > P > .3)

Despite the limited degrees of freedom the control slope is significant. This is probably related to the degree of respiratory instability present - the consequence of dyspnoea - when a greater part of the variation in $P_a CO_2$ is to be attributed to ventilation than under eupnoeic conditions. The post drug slope, despite the larger number of observations, is not significant ($.2 > P > .1$). It is difficult to compare these two regressions because of a highly significant difference between the variances from regression ($P < .001$). The post drug slope is numerically steeper than the control, but, by the use of the method recommended b Bailey (1959) it was shown that this slope difference is not significant ($P > .3$). The calculated difference between the adjusted means is quite marked. However, in view of the marked difference in variances from regression, this estimate of elevation and its attached standard error cannot be accepted without serious reservations. It would seem legitimate to conclude, however, that the loss of significance of slope and the apparent increase in elevation would be consistent with the view that, in patients with left ventricular failure as in normal subjects, the increase in arterial carbon dioxide tension which occurs after administration of morphine is not to be attributed mainly to the fall in ventilation. Since in such patients morphine increases oxygen consumption the observations are entirely consistent with the view that increased carbon dioxide formation plays an important role in causing the recorded increase in $P_a CO_2$.

CASE SUMMARIES

Patients suffering from left ventricular failure

A.O.

A 61 year old male was admitted on 6.11.63 complaining of breathlessness on exertion. In August, 1963, he developed a myocardial infarct for which he was treated in hospital andhad since complained of exertional dyspnoea. On the day of admission he developed acute breathlessness at rest which became rapidly worse. On admission, he was intensely breathless, orthopnoeic and rather distressed. Advanced signs of left heart failure were present. Chest x-ray showed some cardiac enlargement with appearances of pulmonary congestion. Electrocardiogram showed no evidences of further infarction. He was studied on 19.11.63. He had been digitalised on the day after admission with considerable improvement though signs of left ventricular failure were still present at the time of study. Digoxin was stopped on the previous day and restarted immediately after the study was completed. He has remained well.

D. McA.

A 30 year old male labourer was admitted on 14th December 1963 complaining of breathlessness on exertion of 4 weeks duration, occasional attacks of nocturnal dyspnoea for some months and swelling of the ankles first noted some weeks prior to admission. At the age of 18, he was refused entry into the Navy because of high blood pressure. There was also a history of sweating and palpitations for 2 years associated with feelings of anxiety. On admission, the blood pressure ranged between 190 - 220 systolic and 120 - 140 diastolic. He was orthopnoeic. The heart was clinically much enlarged, and triple rhythm was heard. At times, pulsus alternans was noted at the wrist. Jugular venous pressure was raised, bilateral basal crepitations were heard and ankle oedema was present. Chest x-ray confirmed the cardiac enlargement and showed also appearances of pulmonary congestion. ECG showed left ventricular hypertrophy and strain. He was studied on 9.1.64 while still in congestive cardiac failure. Later, he was treated with Guanethidine, Bendrofluozide and digoxin. The last named was started on 24.12.63. He has remained reasonably well on this treatment.

R. McI.

A 58 year old male shoemaker was admitted on 29th December 1963 complaining of breathlessness on exertion and tiredness for the preceding 8 months. An elevated blood pressure had been found 8 years previously but treatment with methyl dopa was started only in May 1963. The present admission was intended to secure better control of his hypertension. On admission, he was orthopnoeic and signs of early heart failure were present. Chest x-ray showed cardiac enlargement with pulmonary congestion. Electrocardiogram showed well marked left ventricular hypertrophy and strain. The effects of morphine were studied on 14.1.64 when the signs of heart failure were still present. He was later re-stabilised on Guanethidine but control of hypertension has remained unsatisfactory.

A.M.

A 62 year old male Polish labourer was admitted on 4.3.64 complaining of angina of effort for some months previously. For about 2 years he had complained of exertional dyspnoea and for some months past had had a troublesome night cough. Three days before admission he developed continuous precordial pain. On admission, he was orthopnoeic and showed signs of left heart failure. He was treated as for myocardial infarction though serial electrocardiograms were negative. He was digitalised on admission and studied on 10.3.64. He was then no longer complaining of precordial pain but the signs of congestive heart failure were still present. He has remained well though continuing to complain of exertional dyspnoea and nocturnal dyspnoea.

E.S.

A 71 year old housewife was admitted on 1.4.64 complaining of increasingly severe breathlessness for the preceding 10 - 14 days with ankle swelling. In October, 1962, she developed a myocardial infarct and since then had been maintained on digoxin. About 2 weeks prior to admission increasingly severe exertional dyspnoea appeared so that by the day of admission she was breathless even at rest. She was also orthopnoeic. On admission, severe breathlessness in bed was apparent with orthopnoea and advanced signs of left ventricular failure. Some peripheral oedema was also present. Chest x-ray showed cardiac enlargement with pulmonary congestion. Electro cardiogram showed evidences of old antero-septal infarction. She was studied on 3.4.64. On the following day, her condition deteriorated and she died rather suddenly. Autopsy showed gross myocardial fibrosis, severe coronary artery atherosclerosis and bilateral nephrosclerosis.

A.G.

A 60 year old housewife was admitted on 28.4.64 complaining of increasing breathlessness on exertion with occasional attacks of nocturnal dyspnoea during the preceding 8 months. A left nephrectomy had been performed in 1948 for an "enlarged kidney". On admission, she was orthopnoeic with signs of left heart failure. Blood pressure ranged between 180 - 220 systolic and 105 - 130 diastolic. Chest x-ray showed cardiac enlargement with pulmonary congestion. Electrocardiogram showed evidence of left ventricular hypertrophy and strain with associated myocardial ischaemia. Creatinine clearance was reduced (42 ml/min.). She was studied on 28.4.64 following which she was digitalised. She was later treated with methyl dopa but control of hypertension has never been satisfactory.

CHANGES IN RESPIRATION, OXYGEN CONSUMPTION, CARBON DIOXIDE OUTPUT AND BLOOD GASES AFTER SOLUBLE PHENOBARBITONE

The effects of an intravenous injection of soluble phenobarbitone were studied in 4 normal subjects according to a protocol identical with that used in the experiments with morphine (figure 1). The purpose of the study was to compare the respiratory effects of morphine with that of another drug known to produce drowsiness. The doses of phenobarbitone used were respectively 3.46, 3.64, 3.14 and 3.14 mg/kg. The doses used invariably produced marked drowsiness which was thought to be similar to that produced by 5 or 10 mg/70 kg morphine. Personal particulars of the subjects were set out in Table 1.

Control Observations

The average age in the group, at 51, is somewhat greater than that of the normal subjects in the morphine treatment groups, a non-significant difference.

Minute ventilation and tidal volume are rather lower and respiratory frequency rather higher than in the morphine series. None of these differences is significant. However, oxygen consumption and carbon dioxide output in the phenobarbitone group are significantly lower than in the normal subjects of the morphine treatment groups (Table 27).

The statistics indicate very stable respiratory and metabolic conditions during the control period. The differences noted would not, of course, invalidate comparisons between the effects of these two drugs.

Effects on Respiration
(Tables 28, 29, figure 36)

Over the 60 minute period following drug administration, ventilation usually showed little change. Minute ventilation increased slightly (1 and 2% respectively) in 2 subjects, and fell (3 and 10% respectively) in 2. The fall in ventilation was significant ($P < .001$) in one subject; the other changes were non-significant. The mean depression of approximately 2% over the 60 minute post drug period was far from significant. No evidence of hyperpnoea after administration of this drug was detected (Tables 28, 29, Figure 36).

The mean respiratory frequency over the 60 minute post drug period declined in all subjects, but in 2 the post drug value was nearly identical with the control. The other 2 subjects experienced a significant depression in respiratory frequency. The mean depression in the group of nearly 5% is not significant at .05 level ($.2 > P > .1$). A larger group would probably have yielded a significant result (Table 28, 29, figure 36).

Tidal volume usually increased. In one subject there was a very slight non-significant decrease in tidal volume ; the increasein tidal volume was, in one subject, significant and, in the other 2 non-significant. The mean increase in tidal volume of approximately 3% was far from significant ($.3 > P > .2$).

These results suggested that the drug primarily affected the respiratory frequency and that changes in tidal volume were compensatory in nature. The combined data plotted in relation to time (figure 37) appears to lend support to this surmise. It will be noted that both ventilation and respiratory frequency

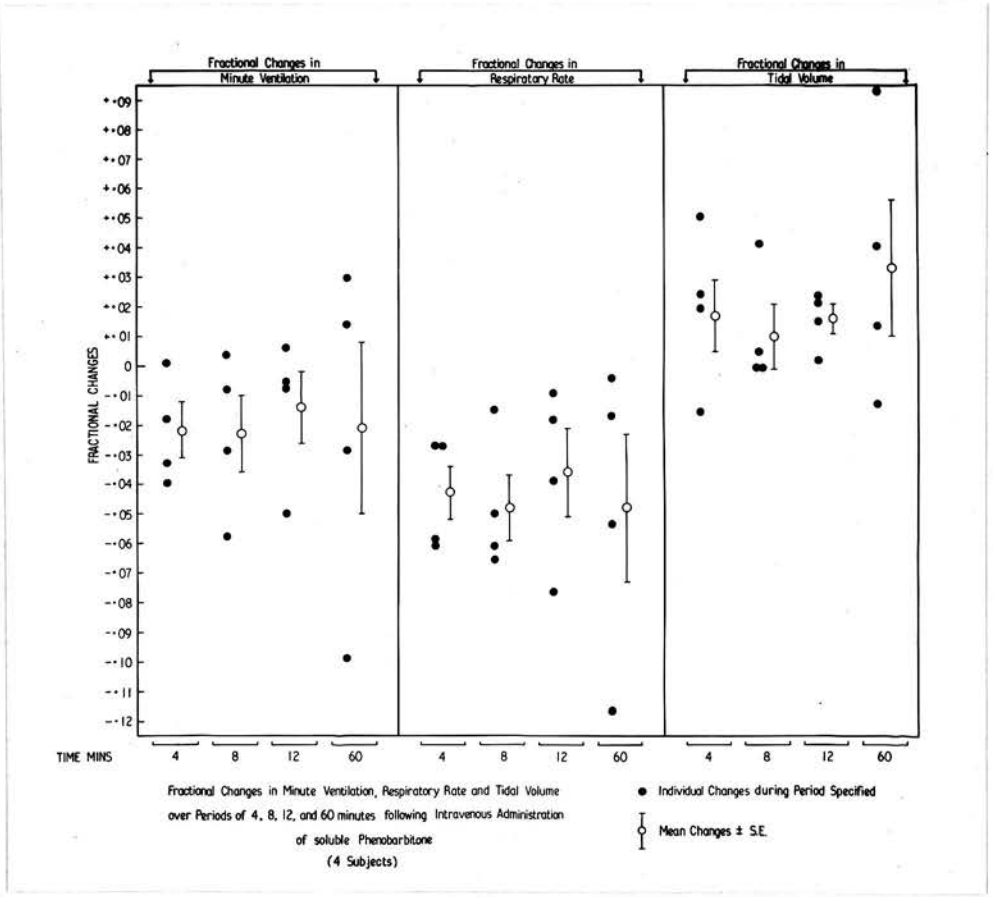


Figure 36

Fractional changes in minute ventilation, respiratory frequency and tidal volume over periods of 4, 9, 14 and 60 minutes after administration of soluble phenobarbitone (four normal subjects).

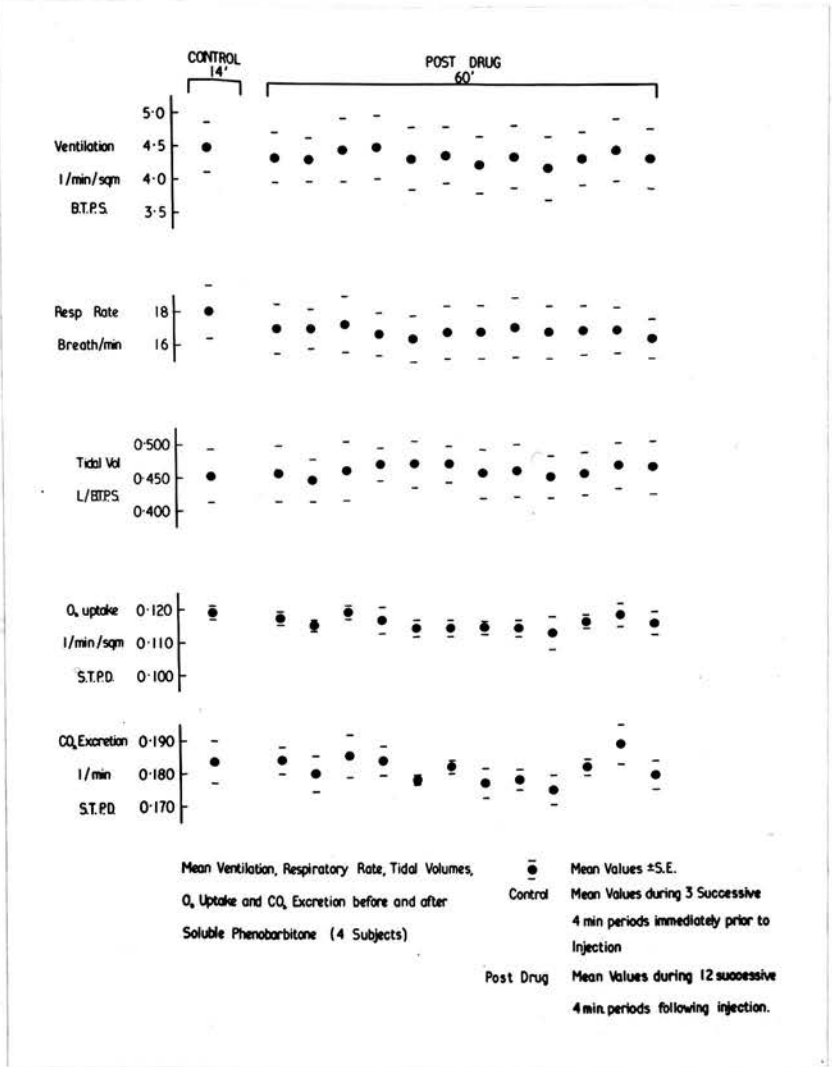


Figure 37

Changes in ventilation, respiratory frequency, tidal volume, O_2 uptake and CO_2 output after soluble phenobarbitone (normal subjects) in relation to time.

fell during the early post drug period. The fall in respiratory frequency is the more marked and persists to some extent throughout the period of observation. Minute ventilation soon recovers from the initial fall and thereafter fluctuates somewhat. The tendency for tidal volume to be increased throughout the post drug period is apparent from the plotted values.

Consequently, the changes in ventilation, respiratory frequency and tidal volume have been studied in relation to the initial three post drug periods. The individual differences from the control value at the end of each of these periods with appropriate sign attached, have been treated, in the usual way, as normally distributed variables and the significance of the mean change tested by means of the standard formula:-

$$t = \frac{\bar{x}}{s\sqrt{n}}$$

a two-tailed test being considered appropriate for the present purpose.

The results (Table 29, Figure 36) emphasise the almost specific effect of soluble phenobarbitone on the respiratory frequency. The mean depression in respiratory frequency at the 4th and 9th minute is, in each case significant; the depression at the 14th minute does not attain significance at .05 level. The fall in ventilation at the 4th minute is not significant at .05 level probably because of the small number of observations. The depression in ventilation at the 9th and 14th minute is, in neither case significant. The tidal volume shows an increase over the same period but this is significant only at the 14th minute.

There seems little doubt, therefore, that soluble phenobarbitone produced an early depressant effect upon the respiratory frequency which tended to persist throughout the 60 minute post drug period. This may be associated, though not necessarily, with a decline in minute ventilation. The tidal volume tends to increase following drug administration - this is presumably a compensatory increase.

The drug caused periodic respiration to appear in all subjects. The rather regular fluctuations evident in the combined data in figure 37 are probably a reflection of this phenomenon.

Effect on Oxygen Consumption
(Tables 28, 29 Figures 37, 38)

Oxygen uptake fell significantly in one subject (J.C.). In this subject, a significant decline in minute ventilation and respiratory rate also occurred. The other 3 subjects showed essentially no change in oxygen uptake as measured over the 60 minute post drug period. The changes in oxygen uptake in relation to time (figure 37) show a tendency to an initial decline followed by recovery and some fluctuation later in the post drug period. These early changes are slight and non-significant. The mean change for the group over the whole post drug period is - 2% approximately, a non-significant change. These observations suggest that soluble phenobarbitone probably depresses oxygen uptake, but that the depressant effect is slight and would require a larger number of observations for attainment of statistical significance. It is to be noted that the mean decline in minute ventilation is of the same order (2%) as the change in

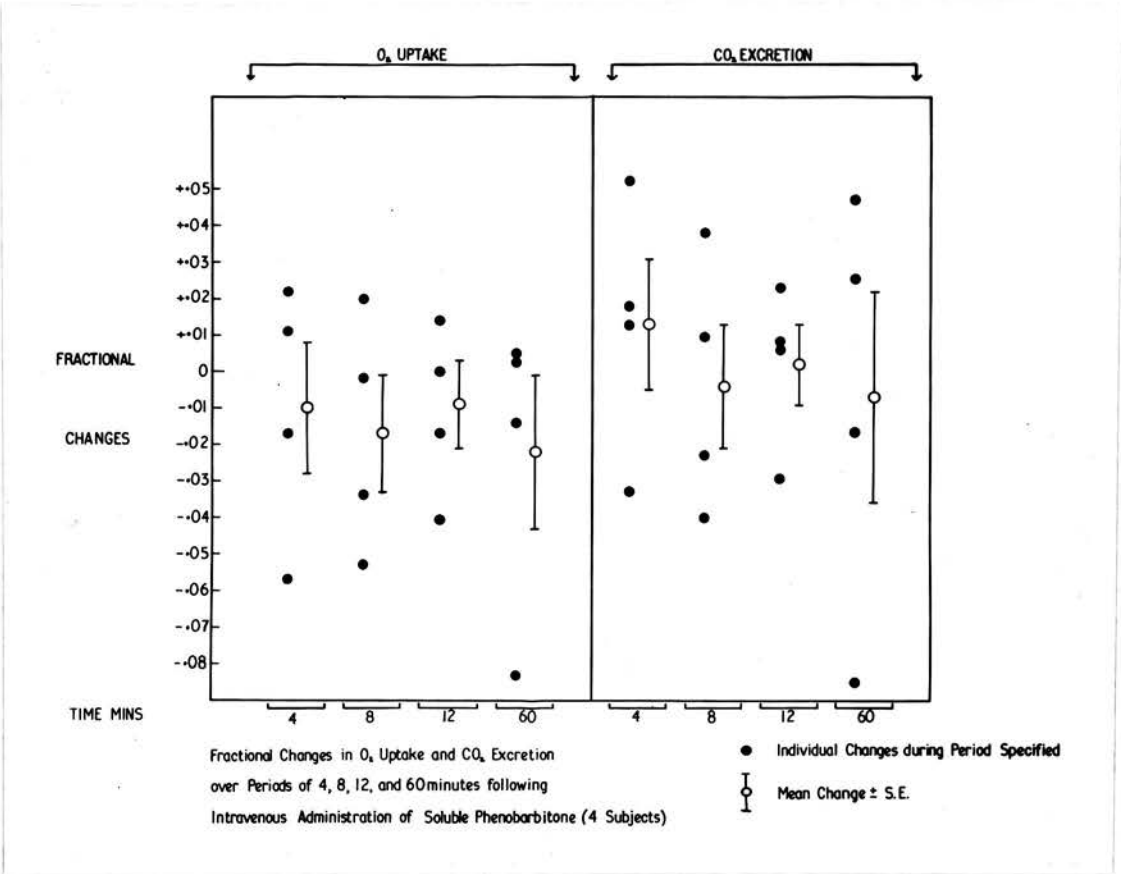


Figure 38

Fractional changes in O_2 uptake and CO_2 output over periods of 4, 9, 14 and 60 minutes after administration of soluble phenobarbitone(four normal subjects).

oxygen uptake - a contrast to the situation obtaining with morphine.

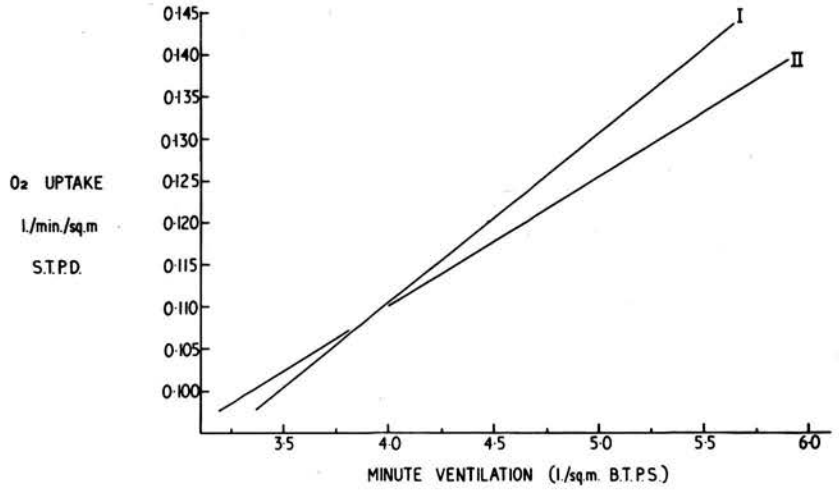
Because both ventilation and oxygen uptake appear to be slightly depressed by soluble phenobarbitone, the changes in oxygen uptake have been considered further, as in the subjects treated with morphine, by regression analysis. Regression statistics relating oxygen uptake and minute ventilation for control and post drug periods separately have been computed, in the usual way, by covariance analysis. Five paired observations are available for estimating the control regression. All the post drug observations - 12 pairs for each subject - have been used. This drug has not caused hyperpnoea and the regressions so computed have been entirely satisfactory.

The control and post drug regressions derived as above stated are given below:-

$\dot{V}_{O_2}/\dot{V}_E$ Regression (soluble Phenobarbitone group)

	r	Degrees of Freedom	S_{yx}	$\bar{Y}$	$a + (b \pm S.E.)$	$\bar{x}$	Control - post drug adjusted mean ± SE.
Control regression	.628	15	.0036	.1207	.0302 + (.0201 ± 0064)	4.499	.0027*** ± .0010
post drug regression	.626	43	.0033	.1163	.0481 + (.0155 ± .0030)	4.394	

Both slopes are significant and neither shows evidence of significant heterogeneity. The post drug slope is some what flatter than control but this apparent slope difference is far from significant. The fitted regressions shown in Figure 39 suggest some difference in elevation and the test of adjusted means shows that this slight difference in elevation (.0027 ± .0010)



O2 uptake related to Minute Ventilation before and after soluble Phenobarbitone I.V. (4 subjects)

Fitted Common Regression Lines :–

I $Y = 0.0302 + (0.0201 \pm 0.0064)X$

II $Y = 0.0481 + (0.0155 \pm 0.0029)X$

Figure 39

Fitted regression lines (derived by covariance analysis) - O_2 uptake related to ventilation before and after soluble phenobarbitone (four normal subjects).

I Control $\dot{V}_{O_2} = .0302 + (.0201 \pm .0064)\ \dot{V}_E$

II Post-drug $\dot{V}_{O_2} = .0481 + (.0155 \pm .0029)\ \dot{V}_E$

is nevertheless very significant (P = .01). This analysis therefore proves that the effect of the drug upon oxygen uptake, though very slight, is nevertheless a real one.

Effects on Carbon Dioxide Output
(Tables 28, 29, Figures 37, 38)

The changes in carbon dioxide output over the 60 minute post drug period have usually been insignificant. In one subject (J.C.) there was a significant depression in carbon dioxide output after drug administration; in this subject, as previously noted, minute ventilation, respiratory frequency and oxygen uptake also fell significantly during the post drug period. The very slight changes in the other 3 subjects (+8, +4.6 and -3.0 ml/min respectively) were, in each case, non-significant. The mean change in carbon dioxide output in the group - a depression of less than 1% - is not significant (P > .8).

The combined data showing the changes in carbon dioxide output in relation to time show that the post drug values tend to fluctuate round the control level (figure 37).

Regression analysis has been applied also to the changes in carbon dioxide output after soluble phenobarbitone, with computation of control and post drug $\dot{V}_{CO_2}/\dot{V}_E$ regressions in the manner described above. The regression statistics are given below:-

$\dot{V}_{CO_2}/\dot{V}_E$ Regression (soluble Phenobarbitone group)

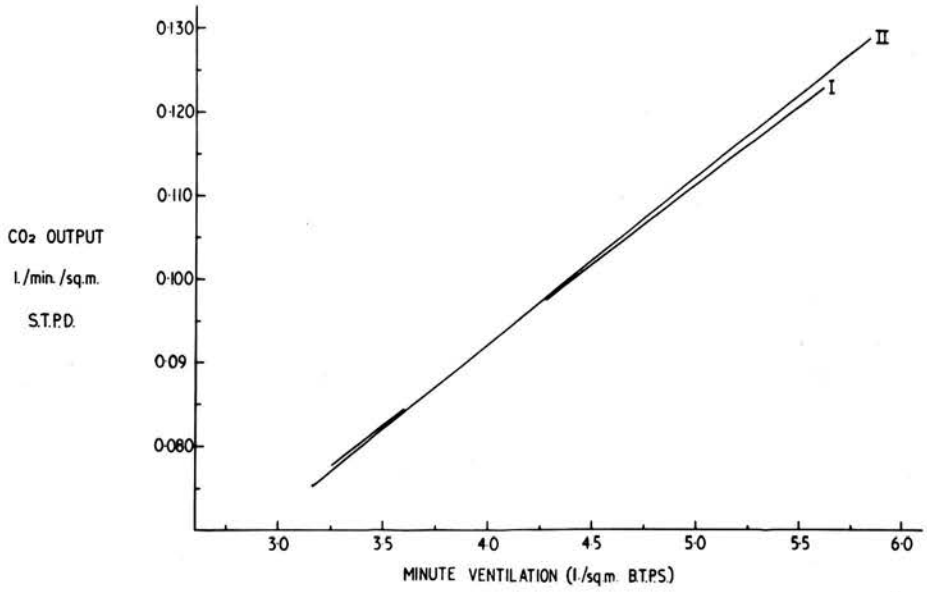
	r	Degrees of Freedom	S_{yx}	$\bar{Y}$	a + (b ± S.E.)	$\bar{X}$	Control - post drug adjusted mean ± S.E.
Control regression	.781	15	.0022	.1019	.148 + (.0194 ± .0040)****	4.499	.0007 ± .0008 (1)
Post drug regression	.791	43	.0027	.1005	.0108 + (.0204 ± .0024)	4.394	

(1) non-significant (.4 > P > .3)

Both slopes are significant and neither shows evidence of significant heterogeneity. Numerically, the slopes are nearly identical and not, of course, significantly different from one another. Both regression lines are, in the statistical sense, identical, as may be readily appreciated from the fitted curves in figure 40. Formal testing of the adjusted means show no evidence whatever of any significant difference (P > .3). These regressions confirm that in the present group, soluble phenobarbitone has no significant effect upon carbon dioxide output and, any change which might be present can be explained entirely by changes in ventilation. Evidently, the depression in oxygen uptake which the drug, without doubt, causes is too small to be reflected by any change in carbon dioxide output.

Effects on Arterial Carbon Dioxide Tension and pH
(Table 30)

Arterial carbon dioxide tension and pH were measured in 3 subjects. $P_a CO_2$ fell significantly in 1 subject. There was a small non-significant increase in each of the other 2 subjects. The arterial pH hardly altered. The increase in $P_a CO_2$ in the sole patient showing a significant decline in ventilation was rather unimpressive at 1.75 mm.Hg.



CO_2 output and ventilation before and after soluble Phenobarbitone I.V. (4 subjects)

Fitted Common Regression Lines derived by Covariance Analysis :–

I Control Regression $Y=0{\cdot}0148+(0{\cdot}0194 \pm 0{\cdot}0040)X$

II Post Drug Regression $Y=0{\cdot}0108+(0{\cdot}0204 \pm 0{\cdot}0024)X$

Figure 40

Fitted regression lines (derived by covariance analysis) - CO_2 output related to ventilation before and after soluble phenobarbitone (four normal subjects).

SUMMARY OF RESULTS, DISCUSSION AND CONCLUSIONS

General Summary of Experimental Results

Normal Subjects

In normal subjects respiration is significantly depressed by each of the four doses administered, although this would not necessarily occur in every subject, particularly in the groups which received the lower doses. There is a linear relationship between the depression in minute ventilation and the dose administered with an apparent tendency for the effect to level off at 15 mg./70 Kg. This latter could not be rigorously demonstrated because of the small size of the 20 mg/70 Kg. group, and the possibility that the greater mean age of the 15 mg/70 Kg. group may have caused this apparent plateau of effect. The slope of the fitted line suggests that doses of morphine much smaller than 5 mg./70 Kg. would be expected to depress minute ventilation (Fig. 4.).

An increase in minute ventilation which lasts 1 - 2 minutes not uncommonly occurred after administration of morphine particularly in the 5 and 10 mg./70 Kg. groups. There is a significant inverse relationship between the dose of drug and the initial change in ventilation so that the smaller doses (5 and 10 mg/70 Kg) are more likely than not to cause an increase in respiratory minute volume of varying degree, and, larger doses (15 and 20 mg/Kg.) more frequently cause an immediate

depression. The initial post drug hyperpnoea is very variable in degree and it is possible that this response is strongly influenced by factors other than the dose of the drug. These factors, possibly, relate to the internal environment, physiological and phychological.

During the first four minutes after injection ventilation declines progressively from these initially elevated or depressed levels.

The respiratory frequency was significantly depressed in the groups treated with 10 and15 mg/70 Kg; in the 20 mg/70 Kg. group this depression did not attain significance at the .05 level, no doubt because of the small size of this group. In the 5 mg/70 Kg. group there was a small non-significant increase in the respiratory frequency.

Tidal volume was significantly depressed only in the 5 and 20 mg./ 70 Kg. groups - in the former, this significant depression followed an initial increase lasting nine minutes. Detailed analysis shows that the effect upon tidal volume is a mixture of depression and stimulation and that depressant effects are predominant in all treatment groups. Stimulant effects are most obvious in the 10 and 15 mg/70 Kg. groups. In the 5 mg/ 70 Kg. group the stimulant effects are apparently restricted to the first nine minutes of the post drug period. In the 10, 15 and 20 mg/70 Kg. groups depressant effects are dominant during the early post drug period and appear to be dose related although this relationship could not be rigorously demonstrated. Stimulant effects upon the tidal volume are not evident at any time in the 20 mg/70 Kg. group although they are

presumably present albeit submerged by the more dominant depressant effects.

Because of the significantly greater mean age of the 15 mg/70 Kg. group, the relationship between depression of minute ventilation and age of subject has been examined. There is a significant regression slope only in the 15 mg/70 Kg. group, the result appearing to indicate a tendency in this group for older subjects to experience a greater depression in minute ventilation. This relationship disappears when the data is pooled by covariance analysis, suggesting either that this holds only for the 15 mg/70 Kg. group - a most improbable situation - or, more plausibly, that the significant correlation is spurious. In an attempt to locate the likely origin of this spurious result it was noted that the 15 mg/70 Kg. group contained an excess of subjects suffering from recent occlusive vascular disease. The question has been left unresolved, and it must be accepted that a possible, though unlikely, cause of the apparent peak effect of the 15 mg/70 Kg. dose is that subjects in this group were, because of age or through unknown clinical factors, more sensitive to the respiratory depressant effects of the drug.

In individual subjects a significant change in oxygen uptake was very uncommon. In each treatment group there was a small mean depression in oxygen uptake which was significant only in the 5 mg/70 Kg. group, but the small differences present among the four treatment groups were not statistically significant. The depression in oxygen uptake was

numerically largest in the 5 mg/70 Kg. group and least in the 20 mg/70 Kg. group. When the changes in all normal subjects are considered together the small mean depression in oxygen uptake is significant.

The more sensitive technique of regression analysis shows that oxygen consumption is affected by morphine independently of its effects upon ventilation. The regression relationship indicates that the drug causes a depression in oxygen consumption because of the decline in ventilation which it induces. In addition and independent of this effect the drug markedly stimulates oxygen uptake and this effect is related to the dose, being least in evidence after 5 mg/70 Kg. and most marked after 20 mg/70 Kg. The drug also exerts an apparently slight depressant effect distinct from that achieved through the depression in ventilation. This last named effect could be demonstrated directly to have occurred only after a dose of 5 mg/70 Kg. but there is evidence, principally from the early changes in oxygen uptake, that it is present also after larger doses. The observations indicate that these stimulant and depressant effects are nearly balanced in the 10, 15 and 20 mg/70 Kg. groups, with the depressant effects predominating slightly. In the 5 mg/70 Kg. group the stimulant effects appear to be confined to the initial nine minutes of the post drug period.

The measurements of carbon dioxide output complement the data on oxygen consumption. The regression relationship indicates a rather closer dependence of carbon dioxide output, than of oxygen uptake, upon ventilation so that approximately 70% of the variation in CO_2 output

during the control period is attributable to ventilation. Carbon dioxide output fell significantly in all the treatment groups but there is no significant dose effect when the 5 mg/70 Kg. group is excluded from consideration. Changes in carbon dioxide output are significantly correlated both with changes in ventilation and changes in oxygen uptake. The partial regression constants indicate that there is a closer dependence upon changes in oxygen uptake than upon changes in ventilation. Regression analysis shows that the drug increases carbon dioxide output independent of any effect on ventilation. It seems certain that this increase is caused by increased endogenous CO_2 formation consequent upon the previously demonstrated stimulant effect upon oxygen consumption. This increase in carbon dioxide output also is dose related. Concurrently, the drug depresses carbon dioxide output because of the depressant effect upon ventilation and, in addition, produces an independent depressant effect upon CO_2 formation presumably related to the analogous depression in oxygen uptake. The measurements of carbon dioxide output thus complement the data on oxygen consumption and confirm that the drug is a potent metabolic stimulant.

Arterial carbon dioxide tensions, measured in 13 subjects, almost invariably increased. The increase in the5 mg/70 Kg. group was not significant, that in the other groups was. After exclusion of the 5 mg/70 Kg. group there is no significant relationship between the increase in P_aCO_2 and the dose of drug administered. Changes in arterial carbon dioxide tension correlate significantly with changes in

oxygen uptake but not with changes in ventilation. The interpretation of these results has been extended by the use of regression analysis. This shows that, while changes in alveolar ventilation are responsible in part for the increase in P_ACO_2 after morphine, the major part of this increase is independent of the changes in ventilation. By this method also the very small increase recorded in the 5 mg/70 Kg. group has been shown to be significant. It would, therefore, appear certain that the greater part of the increase in P_ACO_2 is caused by increased carbon dioxide formation consequent upon the increase in oxygen consumption.

The observations show conclusively that the respiratory effects of all doses or morphine administered are predominantly depressant, though some stimulant effects, particularly - but not exclusively - during the initial post drug period, are probably present in all treatment groups. The effect upon metabolism of doses greater than 5 mg/70 Kg. was predominantly stimulant, and, such depressant effects as were demonstrable were related almost entirely to the depression in respiratory minute volume caused by all doses.

An attempt has been made to find out whether the drug causes any change in the sensitivity of the respiratory centre to changes in arterial carbon dioxide tensions. It can be shown that after morphine higher levels of P_aCO_2 are found for any given level of ventilation, so that, in that sense, the sensitivity to P_aCO_2 has been depressed. Sensitivity, defined as the quotient $\Delta \dot{V}/\Delta P_aCO_2$ has also been considered.

This ratio cannot be measured directly but, with certain assumptions, the computed $\dot{V}_A / P_aCO_2$ control and post drug regressions have been used as an indirect measure of changes in sensitivity. The results show an apparent increase in sensitivity or homeostatic efficiency after the drug which has been interpreted as spurious and probably to be attributed to the fact that the drug produces independent effects upon respiration and P_aCO_2, depressing the former and increasing the latter. From the result it appeared most unlikely that sensitivity as above defined was either depressed or enhanced by the doses used. On the contrary, the regression statistics indicate that normal homeostasis was achieved in all treatment groups studied in relation to the selected new level of alveolar ventilation and arterial CO_2 tensions.

Patients with Left Ventricular Failure

The effects of morphine in six patients suffering from left ventricular failure have been studied. Control observations indicate a larger respiratory minute volume in these patients than in normals but only a slightly larger oxygen uptake. By regression analysis it was shown that the patients suffering from left ventricular failure had a significantly lower oxygen uptake that normals for the level of ventilation achieved. The effects of the selected dose of 15 mg/70 Kg. were qualitatively similar to those recorded in the normal subjects who received the same dose. The fractional depression in ventilation and oxygen uptake was significantly greater than in normal subjects. Even

after administration of morphine patients with left ventricular failure continued to exhibit rather large respiratory minute volumes and a lower oxygen consumption than would be expected in normal subjects for the level of ventilation achieved. The drug also increased oxygen uptake in these patients, the increase being apparently greater than that which occurred in normal subjects who received 15 mg/70 Kg. The changes in CO_2 output were also related, in the main, as in normal subjects, to increased CO_2 formation consequent upon the increase in oxygen consumption. The changes in P_aCO_2 were also probably related mainly to increased CO_2 formation, though, owing to the limited number of observations this could not be rigorously demonstrated. Arterial oxygen tension decreased markedly in two of the three subjects in whom this was measured. Arterial pH fell in all three patients, remaining on the alkaline side of normal in two and falling to acidotic levels in the third.

In contrast to the normal group, an initial increase in ventilation after drug administration to these patients invariably occurred but the rather large mean increase in ventilation at the first post drug minute is only just statistically significant.

Normal Subjects Treated with Soluble Phenobarbitone

Soluble phenobarbitone in the doses used produced marked drowsiness and a slight, though very definite effect upon respiration. The observations show that the drug has a specific effect in depressing the respiratory frequency. A compensatory increase in tidal volume occurs very rapidly so that respiratory minute volume is not necessarily

depressed by the drug except in the early post drug period when such depression appears invariably to occur.

The effect upon oxygen consumption also is very slight but nevertheless real. The mean depression in the group of approximately 2% is similar to the change in minute ventilation. By regression analysis this small change in oxygen uptake has been shown to be very significant. Thus phenobarbitone has been shown to be a metabolic depressant drug in its own right. The drug did not cause a significant decrease in carbon dioxide output in the group - though it did so in one subject. Such changes in CO_2 output as occurred were related entirely to changes in ventilation. Evidently, the change in oxygen consumption is too small to be reflected in changes in carbon dioxide output.

Changes in arterial pH and P_aCO_2 were slight and insignificant even in the subject who experienced a significant fall in ventilation.

There is no evidence that the drug produces hyperpnoea or has other stimulant effects. In particular it depresses rather than stimulates oxygen consumption. The respiratory effects of the drug differ from those of morphine in that it appears to have no depressant effect upon the tidal volume and that compensation for the depressant effects upon the respiratory frequency is very rapidly achieved. Arterial carbon dioxide tension has been largely unaffected, partly no doubt because of the insignificant effect upon respiratory minute volume and partly because, in contrast to morphine, the drug does not increase CO_2 formation.

DISCUSSION

These results have, for the first time, established in quantitative terms the potency of the respiratory depressant effects of morphine in man. The relationship of this depressant effect to the dose of drug has been shown to be linear within the ordinary therapeutic range of dose in man, and not logarithmic, as was apparently the case in some animal studies (Wright and Barbour, 1935; Barlow, 1933). This difference might have been due to the larger doses used in laboratory species. Despite the individual variation in response which is present, the dose/effect regression relationship illustrated in Figure 4 would appear to be a good predictor of the respiratory depressant effects of ordinarily used doses of the drug. The results also suggest strongly, though not conclusively, that the respiratory depressant effects level off at a dose of 15 mg/70 Kg. Such a plateau of effect would be consistent with the results reported by Kokka, Elliott and Way (1965) in rats.

The purpose of the present discussion is to assess the significance of the effects demonstrated in the foregoing sections with the objects particularly of explaining the mode of action of the drug, to consider how, if at all, the respiratory apparatus might compensate for these rather marked effects upon respiration, and, to examine any implications which these results might carry in regard to the clinical use of morphine.

Mode of Action of Morphine as a Respiratory Depressant Drug

The observations recorded make it clear that the primary effect exerted by the drug is upon the tidal volume. This may be the only respiratory depressant effect evident and may occur in the absence of significant change in minute ventilation or respiratory frequency. A dose of 5 mg/70 Kg. has been noted to cause a significant depression in tidal volume with a slight and non-significant increase in the respiratory frequency. Individual subjects treated with this dose almost invariably experienced a fall in tidal volume, usually not associated with any significant change in respiratory frequency and, not necessarily accompanied by any depression, significant or otherwise, in respiratory minute volume. In the other treatment groups, as noted previously, the earliest respiratory effect - extending approximately over the initial 14 minutes following drug administration - is a dose related depression in tidal volume. These observations thus establish that the basic mechanism through which respiration is affected is by means of a depression in the tidal volume. In this respect morphine differs from soluble phenobarbitone which, in doses producing marked drowsiness, depressed respiratory frequency and, usually, caused tidal volume to increase.

Doses of morphine greater than 5 mg/70 Kg. markedly depress respiratory frequency and it seems likely that the effects of the drug upon tidal volume and respiratory frequency are additive. This is shown by the fact that, although the tidal volume tends to increase somewhat

during the later post drug period in the 10 and 15 mg/70 Kg. groups the effects upon tidal volume remain throughout, in all treatment groups depressant. This additive effect is probably responsible for the linear relationship between minute volume depression and dose of drug, the rather steep slope of the regression line, and, in part explains why morphine is so potent a depressant of respiration.

If the effects of the drug upon tidal volume and respiratory frequency were linear over any considerable period of time after administration, it is evident that morphine would be too dangerous a drug for widespread routine clinical use. Fortunately, this is not so. The effect upon tidal volume, although without doubt the primary respiratory effect of the drug, is linearly related to the dose administered only during the early post drug period. Thereafter, in the 10 and 15 mg/70 Kg. groups and probably also in the 20 mg/70 Kg. group, compensatory mechanisms which increase the tidal volume, or at any rate, inhibit any further decline are clearly in evidence. It is, further, likely that these compensatory mechanisms operate from a very early period. Thus, the mean tidal volumes over the 60 minute post drug period in the 10 and 15 mg/70 Kg. groups are, in fact, larger than those of the 5 and 20 mg/70 Kg. groups. Respiratory frequency is most depressed by 15 mg/70 Kg. One explanation of these relationships would be that the breath volume and the respiratory frequency are not only separately influenced by the drug but also react separately in compensation.

It follows, therefore, that the effects of morphine upon breath

volume are seen in least mixed form in the later post drug period after 5 mg/70 Kg. The primary changes in tidal volume and respiratory frequency in all other treatment groups are, to a considerable extent, attenuated by the compensatory increase which occur in both.

It is desirable to consider whether the respiratory depressant effects of morphine are due to the effect of the drug upon the state of alertness or whether these two are unrelated. The measured respiratory effects of soluble phenobarbitone - a drug which in all cases induced moderate to marked drowsiness - suggest that drug induced drowsiness would not per se cause any marked depression of ventilation. In any event, this drug has a fairly specific, though rather slight, depressant effect upon the respiratory frequency. Thus, the respiratory effects of soluble phenobarbitone are in no way comparable with those of morphine.

The respiratory changes which occur during natural sleep or drowsiness provide interesting data for comparison with the effects of morphine. It has been known for some time that respiration is depressed during sleep. Magnussen (1944) first showed that during sleep alveolar carbon dioxide tension increased and the respiratory minute volume fell. Many other workers have subsequently shown that ventilation is significantly depressed during sleep or drowsiness, that alveolar or arterial CO_2 tension is increased and that the ventilatory response to carbon dioxide is diminished (Robin, Whaley, Crump and Travis, 1958; Reed and Kellog, 1958; Birchfield, Sieker and Heyman, 1959; Bülow and Ingvar, 1961; Bülow, 1963).

Ingvar and Bülow (1963) and Bülow (1963) showed very conclusively by continuous monitoring of ventilation, P_ACO_2 and of the state of wakefulness by E.E.G., that changes in the state of wakefulness are very rapidly reflected in changes in ventilation and $P_{A_c}CO_2$. While, during the steady state of normal alertness, only minor changes were found in ventilation and P_ACO_2, the former immediately fell and the latter increased when the state of alertness was depressed.

Oxygen consumption was also markedly depressed during sleep in one study (Robin, Whaley, Crump and Travis, 1958). However, in another study (Bülow, 1963) the reported changes in oxygenuptake were more variable.

81 The measured changes in ventilation and arterial or alveolar carbon dioxide tensions reported during sleep by authors publishing detailed observations, as compared with the waking state have been summarised in Table 31. These may be compared with similar changes following the administration of morphine in the present study (Tables 11, 17; Figs. 2, 3, 26). With the exception of the report by Birchfield, Sieker and Heyman (1959), the depression in minute ventilation has been greater during sleep, and the increase in P_aCO_2 or P_ACO_2 comparatively less than that recorded following administration of morphine. In the only report providing readily accessible data (Robin, Whaley, Crump and Travis, 1958) the depression in oxygen uptake has been considerably greater during sleep than that recorded following any dose of morphine used in the present experiments.

Birchfield, Sieker and Heyman (1959) and Bülow (1963) both report a marked fall in tidal volume during sleep associated with a slight average increase in the respiratory frequency. In the former study the tidal volume fell markedly in each subject during sleep, the respiratory frequency usually showing a slight increase and, only rarely declining.

Bülow (1963) noted also that the transition from wakefulness to uninterrupted sleep was never abrupt and during this period respiration and E.E.G. evidences of alertness fluctuated somewhat. This recalls the situation existing during the initial 14 minute post drug period when ventilation and oxygen uptake are somewhat unstable in all treatment groups.

It is thus evident that there are striking resemblances between the primary respiratory changes induced by morphine and those which occur as the result of sleep. In both states there is a marked fall in ventilation caused primarily by a depression in the tidal volume. This is associated with an increase in P_aCO_2. The respiratory minute volume depression during sleep has, in the reported studies, usually been appreciably greater than those caused by morphine in the present study and the increase in alveolar or arterial carbon dioxide tension rather less, having regard to the degree of respiratory depression. This difference is probably related to the fact - demonstrated for the first time during the present experiments - that morphine increases oxygen

uptake and, in consequence, endogenous CO_2 formation. The evidence indicates that these usually decline during sleep. An unstable transition state is also common to both conditions.

These changes are, in each instance, entirely different from those which follow administration of soluble phenobarbitone. Thus, the state of sedation per se has nothing to do with the respiratory effects of morphine. These latter apparently relate to the activation of mechanisms which normally operate during sleep so that, under morphine narcosis, respiratory depression becomes dissociated from sleep - a circumstance which accounts for some of the unique properties of the drug.

These primary effects of morphine are exhibited in unmixed form only during the later post drug period after a dose of 5 mg/70 Kg. The effects caused by the larger doses, consisting of the additive effects of depressant influences upon tidal volume and respiratory frequency do not resemble the respiratory changes seen during any state of drowsiness or sleep. Indeed, they do not resemble the respiratory changes attributed to any family of drugs mentioned in the literature.

The above conclusions are strengthened by consideration of the relationship between the depression in the state of alertness caused by morphine andthe corresponding changes in ventilation and oxygen uptake.

The state of alertness was depressed by morphine in every subject. Usually, overt signs of drowsiness appeared within five minutes of drug administration, though occasionally a longer interval

elapsed. From the written records kept during each experiment, Tables 32 and 33 have been prepared. These attempt to relate the changes in alertness, to the dose of drug administered and to changes in ventilation and oxygen consumption. Although it appears that the larger doses do cause a somewhat greater depression in the state of alertness, this relationship is by no means striking. Computation of Chi^2 is, unfortunately, not strictly permissible because of the small numbers expected in each cell[1].

In Table 33 the changes in ventilation and oxygen uptake have been placed in ascending order of magnitude of depression with the corresponding rating for alertness underneath. There appears to be no obvious relationship between these changes and the depression in the state of alertness as recorded.

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1 Chi^2 so computed = 5.735, with 6 degrees of freedom- P = .50, nearly.

Significance of Hyperpnoea Following Morphine

The initial hyperpnoea which occurs after doses of 5 and 10 mg/ 70 Kg. will now be discussed. There is little doubt that this is an authentic drug effect. This may be inferred from the very striking inverse relationship to the dose administered (Fig.10) by the absence of the slightest trace of such an effect after the administration of soluble phenobarbitone, and, the almost invariable occurrence at this time, in all treatment groups - whether or not hyperpnoea occurs - of sensory symptoms, mainly paresthesiae involving the head, upper extremities and upper portion of the trunk. It seems likely that factors other than the dose administered contribute to the increase in ventilation during the initial post drug period. The relationship, albeit slight and statistically non-significant, to the variability of the control ventilation and, particularly, the fact that hyperpnoea occurred in all patients with left ventricular failure in contrast with its rarity among normal subjects treated with the same dose - these suggest that respiratory instability during the control period probably influences the response.

Hyperpnoea after morphine administration has been occasionally noted, usually without comment, by other workers. Among the normal subjects reported in the present study, the phenomenon has been regularly associated with an increase in oxygen consumption. There seems little doubt that this initial stimulant effect must be the cause of the increase in cardiac output not infrequently noted immediately after

administration of morphine (Drew, Dripps and Comroe, 1946; Fejfar, Bergmann, Fejfarova and Valach, 1957).

Since morphine is a potent liberator of histamine (Feldberg and Paton, 1950; Nasmyth and Stewart, 1950) it would be useful to consider whether this substance might be responsible for the phenomenon. The time of onset - approximately 15-20 seconds after injection - would be consistent with an histamine effect. Also, histamine causes over-breathing and increased cardiac output and oxygen consumption (Lindell, Soderholm and Westling, 1964). However, if histamine released endogenously were the cause of these events, the effects should be related to body stores of histamine and not at all to the dose of drug. It is possible that this is not a crucial objection. If the drug depresses breath volume in its own right and concurrently released histamine which increases ventilation, it is possible that the latter effect might be dominant at lower doses and that the former might prevail after the larger doses. This cannot be ruled out, though the argument is rather unconvincing. Would histamine stores be larger in persons with less stable ventilation, for example, patients suffering from left ventricular failure?

Could this initial hyperpnoea be truly part of the respiratory effects of the drug? This could well be the case. The initial effects of the drug are clearly exerted at a very sophisticated level of respiratory control - the master which fixes the breath volume. Possibly the drug in its initial impact upsets the orderly handling and processing of data;

so that facilitatory and inhibitory impulses whether deriving from physiological causes such as pulmonary congestion in heart failure or histamine release after morphine, or from psychological causes such as anxiety, are for a brief period undamped. Of interest in this connection is the observation of Seed, Wallenstein, Houde and Bellville (1958) that the magnitude of drug effect appeared to be inversely proportional to the alveolar P_{CO_2} defining the position of their control curve.

These notions are, of course, somewhat speculative but are useful working alternatives to the rather inadequate hypothesis of histamine release.

Morphine as a Stimulant Drug

The evidence obtained in the present study that morphine has stimulant properties will now be reviewed. Apart from the initial period of hyperpnoea referred to previously, in some subjects associated with very transient feelings of apprehension, there were no overt evidences of drug stimulation in any subject.

The regression methods applied in the previous section provide a method of separating the changes in oxygen uptake caused by changes in ventilation from those due to other causes. The estimates of r^2 (Table 15) indicate that under the experimental conditions approximately 35 - 50% of variation in oxygen uptake is due to ventilation. Clearly, therefore, a drug with the potent effects upon ventilation described in the preceding sections should have caused a considerable fall in measured oxygen uptake. Contrary to this expectation, it has been shown that the decline in measured oxygen uptake has been very small, and, paradoxically, greatest in the group which received the smallest dose. This discordance between changes in ventilation and changes in oxygen uptake has been stressed by Krueger (1955). The present study has shown that this can be satisfactorily explained.

The results suggested that the effect of morphine, in the doses used, was threefold. First, it must be assumed from the regression relationship (Table 15), that the drug depressed oxygen uptake because of the depression in ventilation it produced. Secondly, there was an independent depressant effect, presumably due to central "sedative" effects, which, however, could be shown to have occurred only during the later post-drug

period after 5 mg/70 kg. Thirdly, doses of 10, 15 and 20 mg/70 kg stimulated oxygen uptake, at least during the later 45 minutes of the post drug period, independent of any effects attributable to the change in ventilation. The analysis suggested that this last named effect is dose related. Consequently, because of these simultaneously occurring and opposing effects, the net effect of morphine in doses of 10, 15 and 20 mg/70 kg was no more than a slight fall in the measured oxygen uptake (Table 11). These opposing actions would explain the discordance between the change in ventilation and the change in oxygen uptake, and thus the paradox that the smallest dose administered caused the greatest depression in oxygen uptake. Further, in the 5 mg/70 kg group, an increase in oxygen uptake occurred only during the initial 9 minutes of the post drug period, when there occurred also, for part of this period, an increase in ventilation.

Proof that morphine stimulates metabolism does not rest solely on the foregoing analysis of the changes in measured oxygen uptake after drug administration. The measured changes in carbon dioxide output and arterial PCO_2 provide excellent collateral evidence in support. Thus, it was shown that while changes in carbon dioxide output were, in part, and as would intuitively be expecte related to the decline in ventilation, regression analysis demonstrated that there was, simultaneously, an apparent increase in CO_2 output which was independent of any changes due to the depression in ventilation. These observations are best explained by the assumption that an increase in endogenous CO_2 formation occurring simultaneously with the decline in ventilation, limited the measured fall in carbon dioxide output. Further, the present study has shown that the measured increase in $PaCO_2$ after morphine is more closely related to the

afore-mentioned increase in metabolism than to respiratory depression[1]. The control regression relating arterial PCO_2 and alveolar ventilation (Fig. 29) clearly indicates how little arterial carbon dioxide tension would have increased if the drug had no greater respiratory depressant effects than those demonstrated.

The notion that morphine increases oxygen uptake, though seemingly novel, is consistent with certain other reported observations. As pointed out in the review of the literature, a measured increase in oxygen uptake has, on occasion, been recorded after morphine administration, both in man and in laboratory species. The effects of morphine upon body temperature, which have been fully reviewed by Reynolds and Randall (1957) are also consistent with the view that morphine, in some species, causes an increase in heat production. However, the net effect upon body temperature and heat production in man and in most laboratory species, has, in the majority of studies reviewed, been a variable decline. These apparently contradictory findings reported in the literature could be explained, in part, by the three-fold effect of the drug upon metabolism demonstrated in the present study.

The hyperglycaemic action of morphine, which has long been known to occur in man and in laboratory species (Reynolds and Randall, 1957) would also be consistent with the hypothesis that the drug is a metabolic stimulant.

There remains to be considered how the increased metabolism induced by morphine might be achieved. Firstly, it is possible that these effects, like those upon respiration, are centrally mediated. There are other known effects

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[1] See pages 105 - 107

of the drug, which appear to involve stimulatory rather than depressant functions, namely, the release of ACTH and of anti-diuretic hormone, both of which appear to be centrally mediated (de Bodo, 1944; Nasmyth, 1954). Nevertheless, it is, on present information, very difficult to explain how the drug might simultaneously depress some systems and stimulate others. It may be of relevance, however, to point out that some central nervous system may be of relevance, however, to point out that some central nervous system lesions produce simultaneous depression of one type of function and exaltation of another - for example, the co-existing voluntary motor deficit and increase in muscle tone noted after lesions of the pyramidal tracts and in paralysis agitans.

Another possibility is that endogenously released histamine may be responsible, in part, for the metabolic effects of morphine. In experimental animals morphine is known to be a potent liberator of histamine (Feldberg and Paton, 1950; Nasmyth and Stewart, 1950). Although liberation of histamine has never been shown by direct measurement to occur in man, such liberation is likely. At any rate, certain phenomena occurring after administration of the drug, namely, conjunctival and palpebral erythema, puruitus, borborygmi and flushing of the face and upper part of the trunk, are consistent with histamine effects. Further, histamine causes hyperpnoea, increases measured oxygen uptake in man (Lindell, Soderholm and Westling, 1964), and is known in laboratory species to stimulate adrenal medullary and cortical activity (Evans, Nasmyth and Stewart, 1952; Nasmyth, 1954). It is thus possible that the early hyperpnoea observed in many patients and the dose related increase in oxygen uptake may, in part, be attributable to histamine endogenously released by the drug. However, since histamine is very

rapidly destroyed in the body, such release would not explain the sustained increase in metabolism recorded after the larger doses.

The peripheral vaso-dilatation so regularly produced by morphine would be a source of heat loss. Even though body temperature has frequently been reported to be lowered by the drug (Reynolds and Randall, 1957), the heat loss so caused might well induce a compensatory increase in metabolism. It cannot be stated whether or not this does occur. It would be useful to find out whether any increase in metabolism occurs after administration of vaso-dilator drugs devoid of narcotic effects, for example papaverine; and, also, whether attempts to minimise heat loss would affect the increase in oxygen uptake caused by morphine. It would be important too to restudy in man, the effects of morphine upon body temperature since it is not known whether the recorded effects are to be attributed to a central action on temperature regulation or to increased heat loss secondary to peripheral vaso-dilatation.

In conclusion, it must be admitted that, while the inference that morphine increases oxygen uptake and endogenous carbon dioxide formation has been fully supported by the data presented, a satisfactory explanation of the manner in which this is achieved must await the acquisition of additional data. In particular, it would be important to study, in the human, other indices of metabolic stimulation particularly changes in blood sugar and free fatty acid levels, and, to measure directly changes in adrenal medullary and cortical function after administration of morphine to human subjects.

Significance of the stimulant effects of morphine

It is evident from the observations presented that morphine, in doses greater than 5 mg/70 kg, exerts a sustained stimulant effect upon metabolism pari passu with its depressant effects upon respiration. Consequently, the former effect must, to some extent, antagonise the latter and there is much evidence that this occurred. For example, it has been shown that further depression in tidal volume was arrested and some increase occurred in the 10 and 15 mg/70 kg groups. The apparent levelling off of the effect upon respiratory minute volume at 15 mg/70 kg is likely also to have been due to this antagonism between the two independent drug effects. Miller, Gilfoil and Shideman (1955) working with rabbits and Kokka, Elliott and Way (1965) working with rats also report a similar tendency for large doses of morphine to become decreasingly effective in depressing respiration.

Thus, it appears conclusively to have been shown in the present study that morphine is its own antidote, so far as respiratory depression is concerned. It is an astonishing and unique situation that the same drug should, as entirely independent effects, depress the state of alertness and respiration and stimulat e metabolism.

The idea that morphine produces a mixture of depressant and stimulant effects which antagonise each other was first formulated by Tatum, Seevers and Collins in 1929. These workers pointed out that, while monkeys treated with very large or moderate doses of morphine

frequently died in convulsions or depression respectively, animals treated with intermediate doses appeared to fare better. From this it was inferred that in these surviving animals the stimulant effects "pretty well" counterbalance the depressant effects, thus serving as an antidote. As a result of experiments on a variety of laboratory species Tatum, Seevers and Collins concluded that 'morphine has a dual effect consisting of a strange mixture of simultaneous stimulation and depression on different parts of the central nervous system.' They suggested that manifestations of stimulation were referable 'directly or indirectly to increased activity of the cord and certain regions of the brain (miosis, vagal slowing of the heart and, after larger doses, marked direct or indirect reflex excitability of the cord).' They made the important point from their own experiments that the experimental animals (rabbit, cat, dog) die after a period of convulsions and that the depression caused by the smaller doses is not of sufficient depth to cause death.

Neither the experiments of Tatum, Seevers and Collins (1929) nor others reported in laboratory species are comparable with those reported in the present study. The doses of morphine used were massive by comparison with those ordinarily used in man or administered during the present series of experiments. The marked overt signs of stimulation noted in laboratory species were not witnessed in our own studies nor have such effects been documented in the literature in human subjects.

Nevertheless, the views of these workers appear to be essentially correct. In so far as the effects of the drug in man are concerned, the position may be restated as follows. Morphine, among its other effects, independently depresses respiration and the state of alertness and stimulates metabolism. The respiratory depressant and the metabolic effects are each related to the dose administered. These stimulant effects upon metabolism could well be responsible for the compensatory changes in tidal volume and respiratory frequency which were shown to occur after administration of doses in excess of 5 mg/70 kg. They might also be responsible for the apparent - probably real - tendency for the depression in respiratory minute volume to level off at 15 mg/70 kg, and would presumably also antagonise the depressant effects upon the state of alertness.

It must not be thought that the stimulant effects upon metabolism are solely responsible for limiting the degree of respiratory depression caused by the drug. Other intrinsic central mechanisms must presumably also exist - these appear to be very effective in limiting the respiratory depression caused by soluble phenobarbitone.

While some part of the increased oxygen uptake caused by morphine - particularly that during the early post drug period - may have been secondary to adrenal medullary stimulation from released histamine, this cannot account for the sustained increase in metabolism which was recorded after all doses larger than 5 mg/70 kg. It is very probable that, like the respiratory depressant effects, this stimulus to increased metabolism is

centrally mediated. Nasmyth (1954) and Briggs and Munson (1955) have reported good evidence that, in rats, the drug acts centrally to cause release of ACTH. It is also known to act centrally upon the hypothalamo-hypophyseal system to inhibit water diuresis (de Bodo, 1944). It is to be noted that all these effects of morphine relate to interference with a very sophisticated control mechanism. Possibly, this might apply also to its analgesic effects. There is no peripheral or medullary mechanism which would adequately explain any of these effects and no hypothesis based on some single locus of action would fit the facts. Although the observed effects of morphine appear to differ from one another in quality and direction, it is not necessary to postulate a different mode of action centrally for each of these effects individually.

Similar apparently contradictory effects of established central nervous system lesions are the rule rather than the exception and there seems no reason why this should not also occur with the temporary and reversible lesions of drug intoxication. For example, the statement that 'lesions of the basal nuclei frequently depress voluntary motor function while stimulating muscle tone and involuntary activity' is, formally true, but, as it happens to be known, valueless in practical terms.

These considerations perhaps indicate why the search for analgesic members of the opiate family of drugs which are free of respiratory depressant properties or addiction liability has been entirely unsuccessful. It is to be feared that the search may be as hopeful as that for perpetual terrestrial motion.

Mode of Action of Morphine in Patients with Left Ventricular Failure

The respiratory and metabolic effects of morphine in the group of patients suffering from left ventricular failure will now be evaluated. As a group these patients exhibited a larger respiratory minute volume and oxygen consumption prior to drug administration than normal subjects. There was evidence of some degree of respiratory instability but they were metabolically no less stable than the normal group.

Despite a considerably larger respiratory minute volume during the control period the oxygen consumption was only slightly greater than that of the normal group. It was shown by regression analysis that the oxygen uptake in the group of patients suffering from left ventricular failure was significantly less than that of the normal group in relation to the level of ventilation achieved (Fig. 34, 35). Since the oxygen cost of increased ventilation and the work of breathing at rest are greater than normal in patients with congestive cardiac failure (Cherniack, Cuddy and Armstrong, 1957; Hoeschen, Gold, Cuddy and Cherniack, 1962), the energy expended on pulmonary ventilation must, therefore, be a considerably greater proportion of the total energy requirements than is normally the case. This observation is consistent with the theoretical calculations of Otis, Fenn and Rahn (1960).

The effects of morphine in this group of patients consisted of, (1) the relief of dyspnoea as a subjective sensation (despite the persistence of relatively high levels of respiratory minute volume), (2) a marked fall in

ventilation and oxygen uptake, and (3) increased P_aCO_2 and decreased P_aO_2.

There can be no question of the effectiveness of morphine in relieving the discomfort of dyspnoea and, probably, no other family of drugs will achieve this end as efficiently.

Although the decline in ventilation is significantly greater than that which occurred in normal subjects who were treated with the same dose of drug, tachypnoea with relatively large respiratory minute volumes persist in these patients (Table 24; Fig. 32).

The changes in oxygen consumption cannot be considered as qualitatively different from those occurring in normal subjects. The net decline in oxygen uptake is significantly greater than that which occurred in the normal subjects treated with the same dose. This is, no doubt, to be explained by the significantly greater decline in ventilation. In this group also, the drug stimulates metabolism. The increase in oxygen uptake attributed to the drug as an independent effect is apparently greater in this group than in the normal treatment group.

As in normal subjects also it seems likely that the increase in oxygen consumption contributes appreciably to the increased arterial carbon dioxide tension after morphine.

Patients with left ventricular failure treated with morphine would benefit by the reduction in the energy requirements for breathing. While the drug stimulates metabolism, the net effect is a decrease in oxygen

consumption consequent upon the marked fall in ventilation. In patients suffering from acute pulmonary oedema the fall in oxygen uptake would, of course, be even greater than that recorded in the present study. Thus the drug decreases, very considerably, the proportion of total energy requirements devoted to maintaining pulmonary ventilation. While patients will, no doubt, benefit from this reduction, it is not known whether this will necessarily contribute appreciably to relief of pulmonary congestion.

It is possible that patients with marked tachypnoea such as is seen in acute left ventricular failure might derive immediate benefit from the decline in minute ventilation caused by the drug. Rowe, Castillo and Crumpton (1962) reported that in human subjects active hyperventilation caused significantly reduced coronary blood flow with reduced coronary sinus oxygen tension - findings which they interpret as indicating probable myocardial hypoxia. Yamamoto and MacIver (1960) reported also that sustained high levels of ventilation induced by continuous CO_2 infusion in rats caused pulmonary oedema and heart failure.

Be that as it may, some saving in energy expended has been achieved at a price which has now to be evaluated. The fall in ventilation and, even more, the increased CO_2 formation consequent on the metabolic effects of morphine will cause a marked increase in P_aCO_2. This occurred in the 3 patients in whom arterial gas tensions could be measured and, presumably, would invariably occur. Many patients with left ventricular failure,

particularly those severely dyspnoeic, would have a low or low normal P_aCO_2 prior to drug administration so that dangerous levels of P_aCO_2 and of arterial pH after morphine would probably not be common (Fig. 30). It is of some historical interest that Fraser (1923) suggested that this increase in CO_2 tension from hypocapnic levels might itself improve cardiovascular function in patients with cardiac dyspnoea.

There seems no doubt, however, that significant or even marked hypoxaemia would develop in patients treated with morphine alone. Whether or not this is an acceptable price to pay would depend upon the aetiology of heart failure and upon the other therapeutic measures concurrently offered. In patients with left ventricular failure secondary to myocardial infarct or ischaemic heart disease marked hypoxia would probably be considered unacceptable. It would be safer to offer such individuals small doses which would relieve dyspnoea but not reduce ventilation markedly. The concurrent administration of oxygen and digitalis would in any case be recommended.

In each of the patients studied, a moderate or marked increase in ventilation occurred immediately after administration of morphine. It has been recorded previously that there is reason to think that respiratory instability during the control period may predispose to the occurrence of post drug hyperpnoea. If this surmise is well founded - as it appears to be - it follows that the majority of patients in left ventricular failure, particularly those with acute pulmonary oedema, will exhibit some hyperpnoea after an appropriate dose of morphine. It seems probable that

this initial stimulatory effect of the drug is responsible for the increased cardiac output reported by Fejfar, Bergmann, Fejfarova and Valach (1957) which these authors mistakenly attribute to a specific action of the drug in patients with low cardiac outputs.

Could this marked initial stimulation contribute to improved cardio-respiratory function? The changes which occur at that time may well convey the impression of dramatic clinical improvement and it is by no means improbable that such improvement does in fact occur. This initial period of hyperpnoea coincides with the flushing of the face and upper extremities which occurs in all subjects treated with morphine intravenously whether or not overbreathing is present. Hyperpnoea, peripheral vaso-dilatation and increased cardiac output during the first minute or two following intravenous administration could conceivably contribute significantly to lung drainage. Because of the greatly increased ventilation hypoxia, where present before administration might be reduced or, at any rate, its inevitable later development is postponed. Thus, time is purchased during which other more slowly acting measures can be offered.

The rapidity with which patients who do benefit improve after administration of morphine intravenously suggests that this may be the chief contribution of the drug to clinical improvement. Other drug effects, particularly the relief of tachypnoea and the consequent fall in the energy requirements for breathing no doubt help over the longer term. Nevertheless the price exacted must be balanced against this saving in oxygen requirements - particularly the inevitable hypoxia.

It is necessary, once more, to stress the point that the clinical use of morphine in left heart failure has never been rigorously evaluated. Such evaluation is needed, particularly since measurements of pressure changes in patients with acute pulmonary oedema after administration of the drug do not always show improvement (Scebat and Lenegre, 1949; Fejfar, Bergmann, Fejfarova and Valach, 1957; Finlayson, Luria, Stanfield and Yu, 1961).

Nevertheless, it is to be expected that morphine will continue to be used in the treatment of left ventricular failure and particularly in the acute type of this disorder. The results of the studies here reported suggest that the improvement to be expected derives mainly from the initial stimulant effect upon ventilation associated with probable peripheral vasodilatation and, in many cases presumably an increase in the cardiac output. Moderately and severely dyspnoeic patients will no doubt benefit, in the longer term, from the reduction in the energy requirements of breathing and from the rapid relief from potentially dangerous effects of hyperventilation itself. Because of the inevitable hypoxia and because other more specific and effective therapy is usually available, the large doses of morphine recommended by traditional teaching (Hamilton, 1955) should probably be avoided. On the basis of the observations on normal subjects, it would appear that doses in excess of 5 mg/70 kg should probably not be offered to patients suffering from left ventricular failure.

GENERAL CONCLUSIONS AND CLINICAL IMPLICATIONS

While the experiments described in the foregoing account have solved some problems relating to the effects of morphine in man, other questions have, perforce, been left without clear answer.

The results reported explain the fact - suggested by clinical experience - that morphine, despite the potency of its clinically unwanted effects, is a comparatively safe drug. In antagonism to the additive effects upon the breath volume and respiratory frequency, the drug fortunately produces simultaneous effects limiting the respiratory depression which occurs after ordinary therapeutic doses so that this does not attain the degree which commonly occurs during natural sleep. Even the very large doses which were routinely used in the past would probably not cause dangerous respiratory depression in fit persons because of the flattening of the dose/effect slope which almost certainly occurs above 15 mg/70 kg. Another reason for the comparative safety of the drug would be that, at the selective altered levels of $PaCO_2$ and breath volume, efficiency of homeostasis is probably not impaired after ordinary therapeutic doses.

On the basis of these results there would be theoretical reasons for supposing that the analgesic effects of morphine are mediated in a manner similar to its respiratory depressant effects. In that event,

it would seem that the optimal dose of the drug for clinical relief of pain would be of the order 5 - 10 mg/Kg. Larger doses, while not likely to carry any significant risk to persons with normal pulmonary function are probably wasteful. In recent years it would appear that the 10 mg. analgesic dose has in practice become a standard for routine use.

A very important result of the study has been the demonstration that increased levels of arterial carbon dioxide tension after morphine are related mainly to the action of the drug as a metabolic stimulant and in relatively slight degree only to the decline in ventilation. This observation would explain why the drug, which does not in normal individuals depress minute ventilation more than occurs during natural sleep, can be dangerous to patients suffering from chronic pulmonary insufficiency. Since such individuals have difficulty - due to established anatomical or functional changes - in eliminating carbon dioxide, the increase in endogenous CO_2 formation caused by the drug will frequently lead to dangerous levels of $P_a CO_2$ and a consequent fall in arterial pH to acidotic levels. That hypercapnia and respiratory acidosis rather than primary respiratory failure is the cause of death in many of these patients treated with morphine is suggested by published clinical descriptions (Samuelsson, 1952). It is noteworthy that, almost invariably, the deaths reported in this publication occurred several hours after the administration of ordinary therapeutic doses of the drug.

In cardiogenic shock also, when a marked metabolic acidosis is frequently present (Mackenzie, Taylor, Flenley, McDonald, Staunton and Donald, 1964; Mackenzie, 1965), the use of morphine may well carry potential dangers. However, there do not appear to be any clinical reports bearing on this point.

The observations on patients suffering from left ventricular failure offer, for the first time, a plausible working hypothesis based on quantitative data. Previous experiments on the effects of morphine in patients suffering from left heart failure - the great majority of modern studies having been performed on patients with mitral valve disease - have been essentially negative. The present study has recorded a modest but very definite advance in two respects. First, it has shown the necessity for a full evaluation of the role of morphine in the clinical management of patients suffering from left ventricular failure; and, secondly, analysis of the continuous measurements recorded has focussed attention upon three possible mechanisms through which clinical improvement, when this occurs, might be mediated.

Most of the objections raised by Krueger (1955) to the generally held opinion that morphine depresses the respiratory 'centre' have been met by the results of the present study. Krueger stressed, in particular, the fact that the respiratory depression caused by morphine was always less than the change in oxygen consumption in laboratory species and in man. He was also puzzled by the occurrence, in some reported experiments, of an increase in respiratory minute volume and

oxygen consumption. These observations are all adequately explained by the results of the present study. Another point to which Krueger drew attention was the fact that repeated doses of morphine administered to laboratory species cause, not further respiratory depression, but stimulation. This is fully explained by our demonstration that morphine is a potent metabolic stimulant and is, in fact, a striking retrospective confirmation of one of the main findings of the present investigation. Krueger was led to conclude that morphine depressed respiration - when this occurred - by depressing metabolism. It is evident, however, that this hypothesis cannot be correct, since it has been conclusively shown in the course of the present investigation that the drug has independent and opposite effects upon respiration and metabolism. In retrospect it would appear that many of the equivocal observations in the past are to be attributed to the practice of administering morphine in repeated doses during the same experiment.

An historically interesting consequence of the present work is that it has been possible to restate the "dual action" hypothesis of Tatum, Seevers and Collins (1929) in relation to man. While the concept of a true dual action appears not to be accurate, the conclusion of these workers that morphine is its own antagonist appears, so far as respiratory depression is concerned, to be essentially correct. It is strange that data in support of their ideas have not previously been obtained from observations on human subjects.

It may seem curious that, throughout this report, no mention

has been made of one of the common respiratory effects of morphine, namely, the induction of periodic or Cheyne Stokes breathing. This omission has been deliberate and for the following reasons. In the present study obvious disturbances of the respiratory rhythm have been noted in the spirometer records only among subjects who received 10 or 15 mg/70 Kg. morphine. In some of these subjects periodic respiration resembling classical Cheyne Stokes breathing developed for varying periods of time. At other times and in other subjects other types of irregular breathing appeared. Similar disturbances were not seen in any of the subjects treated with 5 or 20 mg/70 Kg. Analysis of these disturbances of rhythm is likely to be a difficult problem not capable of solution by the methods used in the present investigation. This problem may be stated in concise form as follows. What is the effect of morphine upon the respiratory cycle and how does this compare with the effects of other drugs and with changes occurring physiologically, for example, during drowsiness and sleep.

Changes in the respiratory cycle cannot be explored adequately by the simple technique of breath enumeration because, while this provides an estimate of the mean length of the respiratory cycle, other variables, for example, the individual cycle lengths, the length of non-breathing periods or pauses and their relationship to changes in the individual breath volumes, cannot be estimated in this way. It is evident that the solution of this problem will require further analysis and, perhaps, additional data. The writer has undertaken some preliminary

work by the method of treating successive individual breath volumes as a continuous time series on the simple assumption that inequalities in the duration of individual cycles can be ignored. Under very steady conditions there is a slow oscillation of low amplitude about a mean value so that, in this sense, periodic breathing is a normal phenomenon of the waking state. This periodicity is essentially unaffected by morphine in a dose of 5 mg/70 Kg. - confirmation, incidentally, that the primary effect of the drug is upon the breath volume and not upon the respiratory cycle. It was found, however, that when less than very steady conditions prevailed - as assessed by the variability of the individual breath volumes - the duration of the cycle length cannot be ignored. Analysis will therefore involve more extensive work than could be undertaken within the limits of the present project.

Although the studies with soluble phenobarbitone were designed to provide more rigorous experimental control for the main project, the results are a useful addition to the rather scanty literature on the respiratory effects of barbiturate drugs. They show very definitely that the rather mild respiratory depressant effects of soluble phenobarbitone are produced by an entirely different mechanism, both from those caused by morphine and from those which occur during natural sleep. The view that barbiturates are potent respiratory depressant drugs (Goodman and Gilman, 1965) does not seem to have been borne out by the results of the present study. However, rather similar results have been published by Eckenhoff, Helrich and Hege (1955) for seconal and by Keats

and Beecher (1952) for pentobarbital sodium. In the former study the drug produced no very definite changes in respiration or P_aCO_2 in the three subjects studied. In the latter, minute volume and respiratory rate, measured in 15 subjects, fell by about two and a half per cent and oxygen consumption by about five per cent one hour after drug administration - findings not very dissimilar from our own. Curiously, in this latter study the respiratory sensitivity to carbon dioxide, as measured by conventional methods, was increased by the drug, despite the definite respiratory depression revealed by the other data.

Finally, the results fully justify the critical attitude shown during the review of the literature towards the use of CO_2 response curves as a measure of drug action. It is evident that the failure to make orthodox measurements of respiratory variables, particularly in relation to time, would have resulted in the loss of very valuable information. The data further cast doubt upon the supposition that morphine causes any change in the sensitivity of the respiratory apparatus in any meaningful physiological sense. Indeed, it would appear doubtful that the study of CO_2 sensitivity curves, as at present computed, serves any useful experimental purpose.

ACKNOWLEDGMENTS

It is a pleasure to record my thanks to my colleagues in the Department and to the technical staff for their help and more particularly to the following.

Miss Edna Grossart, who assisted with the spirometry in the great majority of the studies,

Miss Morag Forsyth and Miss Jeanette Young for performing the blood gas analyses;

Mr James Walker for arranging to provide technicians' services as required and for many acts of kindness too numerous to detail;

Drs. M. George and Alastair McDonald who took the expired air samples during many of the studies.

Dr Trevor Hampton was associated with me during part of the project. His active interest and assistance are gratefully acknowledged.

Dr. Keith Donaldson helped with the preliminary studies which provided the information on which the plan of study was based.

I thank Professor K. W. Donald for providing the facilities and the funds for the project and for many useful discussions relating to the experimental design and the interpretation of the results.

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Table 1

Personal Particulars

Treatment Group	Subject	Age	Anthropomorphic Data			Reason for admission to hospital
			Ht. (cm.)	Wt. (kg.)	S.A. (sq.m.)	
Normal subjects in the treatment groups given morphine (all subjects male unless stated otherwise)						
5 mg/70 kg morphine	W.B.	23	170	56.5	1.64	Renal colic
	F.G.	35	187	71.4	1.94	Peripheral sensory neuropathy
	W.E.	55	170	74.5	1.85	Hypertension Recovered left hemiparesis
	G.R.	46	178	66.3	1.82	Duodenal ulcer
	M.W.	46	169	69.8	1.80	Chest pain of uncertain causation (myocardial infarct excluded)
	J.H.	37	170	67.5	1.77	Hiatus hernia
10 mg/70 kg morphine	A.W.	40	177	72.5	1.89	Myocardial infarct (two weeks before study)
	W.H.	54	165	75.5	1.82	Hypertension
	G.F.	30	173	65.5	1.77	Chronic duodenal ulcer
	W.J.	32	180	80.0	1.98	Hiatus hernia Anxiety symptoms.
	A.McK.	49	187	70.1	1.93	Hypertension.
	W.D.	31	171	65.4	1.76	For investigation of vomiting Mild depressive illness
	J.N.	47	172	74.0	1.86	Hypertension
	R.M.	32	177	62.0	1.81	Ureteric calculus
	I.S. (female)	32	162	84.0	2.04	Hiatus hernia
15 mg/70 kg morphine	J.R.	45	178	71.1	1.87	Duodenal ulcer
	J.P.	65	174	71.8	1.85	Prolapsed intervertebral disc
	J.C.	42	186	84.75	2.08	Myocardial infarct (3 weeks previously)
	A.M.	49	174	74.5	1.89	Hypertension Transient left-sided weakness
	J.McK.	41	173	69.95	1.82	Spastic paraparesis Cervical disc protrusion
	A.N.	65	171	69.5	1.81	Myocardial infarct (4 weeks previously)
	H.S.	52	174	81.5	1.97	Hypertension Recovered cerebrovascular accident (Brain stem)
	W.I.	62	175	76.15	1.91	Cerebellar cortical degeneration
	C.D. (female)	62	152	41.0	1.32	Epilepsy (minor attacks)
20 mg/70 kg morphine	J.R.	42	171	68.5	1.80	Pyrexia of unknown origin
	C.R.	62	167	90.7	1.98	Spastic paraparesis Cervical spondylosis
	J.D.	53	170	66.8	1.76	Epileptiform attack
	W.F.	40	173	67.8	1.80	Viral pericarditis (3 weeks previously)
Normal subjects in the treatment groups given soluble phenobarbitone						
220 mg (3.46 mg/kg)	G.M.	38	171	63.5	1.74	Anxiety symptoms
220 mg (3.64 mg/kg)	A.McD.	60	177	60.5	1.75	For investigation of epigastric pain
255 mg (3.15 mg/kg)	A.M.	44	171	81.0	1.92	Myocardial infarct (2 weeks previously)
212 mg (3.14 mg/kg)	J.C.	62	175	67.6	1.82	Transient right upper limb weakness
Patients in left ventricular failure given morphine 15 mg/70 kg						
	A.O.	61	173	70.15	1.82	Ischaemic heart disease Recent myocardial infarct
	D.McA.	30	168	68.5	1.77	Hypertension
	R.McI.	60	169	65.0	1.73	Hypertension
	A.M.	62	165	59.2	1.64	Ischaemic heart disease
	E.S. (female)	71	165	55.0	1.59	Myocardial infarct
	A.G. (female)	60	154	68.7	1.67	Hypertension

Table 2

Statistics relating to age Control (pre-drug)

Observations in and variability in control ventilation and oxygen consumption

Treatment Group	No. of subjects	Age	Control Respiratory Measurements			Respiratory Exchange Data			Variability (S.D./Mean)			
			Minute ventilation l./sq.m. BTPS	Respiratory frequency (breaths/min)	Tidal volume l./BTPS	No. of subjects	Oxygen consumption l./min./sq.m. STPD	Carbon dioxide output l./min./sq.m. STPD	No. of subjects	Variability in ventilation	No. of subjects	Variability in oxygen consumption
Normal subjects Morphine 5mg/70kg	6	40.33 ± 4.54 (11.11)	4.210 ± .0172 (.3854)	14.29 ± .063 (1.549)	.536 ± .0177 (.0434)	5	.1363 ± .0032 (.0071)	.2097 ± .0051 (.0115)	6	.1013 ± .0232 (.0568)	5	.0345 ± .0118 (.0264)
" 10mG/70kg	9	38.55 ± 3.07 (9.22)	4.745 ± .2201 (.6600)	16.69 ± 1.042 (3.128)	.541 ± .0325 (.0974)	8	.1411 ± .0076 (.0215)	.2209 ± .0107 (.0303)	9	.0788 ± .0136 (.0409)	8	.0237 ± .0055 (.0157)
" 15mg/70kg	9	53.66 ± 3.32 (9.95)	4.677 ± .1573 (.4717)	17.28 ± 1.007 (3.022)	.494 ± .0300 (.0901)	9	.1312 ± .0048 (.0145)	.2023 ± .0112 (.0337)	9	.0585 ± .0089 (.0268)	9	.0276 ± .0043 (.0130)
" 20mg/70kg	4	49.25 ± 5.12 (10.22)	5.198 ± .2274 (.4544)	17.81 ± 1.813 (3.625)	.545 ± .0440 (.0880)	4	.1463 ± .0020 (.0040)	.2218 ± .0052 (.0103)	4	.0561 ± .0064 (.0138)	4	.0261 ± .0088 (.0175)
Totals - All normal Treatment groups in morphine series	28	45.32 ± 2.20 (11.64)	4.674 ± .1095 (.5796)	16.52 ± .569 (3.010)	.525 ± .0157 (.0832)	26	.1376 ± .0030 (.0154)	.2124 ± .0053 (.0270)	28	.0738 ± .0076 (.0404)	26	.0275 ± .0033 (.0169)
Test for departure from homogeneity by analysis of variance		4.155(3,24)	2.936(3,24)				1.089(3,22)	1.170(22,3)		1.810(3.24)		
F values		.025 > P > .01	.1 > P > .05									

TABLE 3

MINUTE VENTILATION, RESPIRATORY RATE, TIDAL VOLUMES, O_2 UPTAKE AND CO_2 EXCRETION ~~(EXPIRED AIR)~~

MEASUREMENTS DURING SUCCESSIVE FOUR MINUTE PERIODS BEFORE AND AFTER MORPHINE 5mg/70Kg

Age Sex Subject S.A. Ht. Wt.	Measurement	Control Periods			Mean Control Values	Post Drug Periods											
		1	2	3		1	2	3	4	5	6	7	8	9	10	11	12
46 yrs. M G.R. 1.82 sq.m. 178 cms. 66.3Kg	Minute Ventilation	4.173	4.236	4.219	4.209	4.359	4.127	3.695	3.818	3.849	3.772	4.076	4.431	4.195	3.949	3.990	4.035
	Respiratory Rate	16.25	16.25	16.25	16.25	18.00	15.75	14.25	14.25	14.25	14.50	14.50	15.25	14.50	14.50	14.00	15.00
	Tidal Volumes	.466	.473	.478	.472	.441	.480	.473	.496	.495	.485	.518	.530	.522	.502	.524	.505
	O_2 Uptake	.140	.143	.141	.1413	.143	.150	.131	.139	.136	.135	.142	.148	.140	.137	.138	.137
	CO_2 Excretion	.204	.211	.207	.2073	.209	.204	.182	.197	.204	.198	.218	.237	.220	.211	.218	.217
23 yrs. M W.B. 1.64 sq.m. 170 cms. 56.5Kg	Minute Ventilation	4.749	4.783	4.530	4.688	5.310	4.248	3.729	4.362	4.158	4.494	5.211	4.285	4.596	4.053	3.939	3.854
	Respiratory Rate	15.00	12.50	13.00	13.50	11.50	12.25	12.75	14.25	14.25	14.75	15.75	15.25	16.50	12.50	12.50	12.75
	Tidal Volumes	.524	.636	.582	.580	.743	.573	.490	.487	.485	.517	.546	.468	.458	.523	.523	.508
	O_2 Uptake	.150	.143	.135	.1427	.152	.152	.133	.148	.136	.139	.143	.130	.138	.140	.118	.136
	CO_2 Excretion	.208	.213	.195	.2053	.239	.190	.162	.190	.179	.189	.215	.179	.185	.182	.156	.171
55 yrs. M W.E. 1.85 sq.m. 170 cms. 74.5Kg	Minute Ventilation	4.521	4.544	4.395	4.487	4.205	4.130	4.069	4.092	4.016	4.092	4.154	4.095	3.832	4.013	3.975	4.029
	Respiratory Rate	15.25	15.75	15.00	15.33	15.50	15.25	15.75	15.00	15.25	15.25	15.50	15.25	15.75	15.50	15.75	16.00
	Tidal Volumes	.556	.538	.541	.543	.493	.504	.483	.502	.491	.499	.501	.498	.453	.485	.472	.471
	O_2 Uptake	.131	.133	.129	.1310	.124	.133	.130	.129	.121	.127	.128	.126	.118	.123	.125	.121
	CO_2 Excretion	.220	.218	.211	.2163	.198	.198	.196	.198	.192	.198	.196	.194	.183	.191	.187	.191
37 yrs. M J.H. 1.77 sq.m. 170 cms. 67.5Kg	Minute Ventilation	3.713	3.254	3.895	3.621	2.984	3.206	3.206	3.214	3.491	3.681	3.523	3.555	3.475	3.356	3.467	3.499
	Respiratory Rate	13.50	10.75	13.00	12.42	8.75	7.00	10.50	11.00	13.25	14.75	14.25	14.00	12.50	12.75	13.50	13.25
	Tidal Volumes	.486	.558	.510	.518	.595	.782	.524	.520	.472	.446	.438	.444	.498	.465	.458	.470
	O_2 Uptake	Analyses technically unsatisfactory															
	CO_2 Excretion																
35 yrs. M F.G. 1.94 sq.m. 187 cms. 71.4Kg	Minute Ventilation	3.846	3.989	3.958	3.931	3.765	3.814	3.750	4.101	3.872	3.808	3.894	3.929	4.101	4.130	4.052	4.237
	Respiratory Rate	11.75	13.25	13.75	12.92	13.75	14.00	13.50	15.25	15.00	15.25	15.00	15.25	16.25	17.75	16.75	16.75
	Tidal Volumes	.641	.577	.544	.587	.525	.511	.531	.506	.488	.488	.506	.503	.482	.454	.474	.494
	O_2 Uptake	.137	.143	.140	.1400	.132	.136	.139	.138	.129	.129	.130	.135	.135	.132	.129	.135
	CO_2 Excretion	.229	.225	.221	.2250	.208	.211	.213	.221	.208	.206	.211	.215	.211	.208	.206	.227
46 yrs. M M.W. 1.80 sq.m. 169 cms. 69.8Kg	Minute Ventilation	4.028	5.077	3.874	4.326	8.009	4.614	4.245	3.719	4.044	3.550	4.290	3.545	4.424	4.039	3.746	4.357
	Respiratory Rate	14.50	17.00	14.50	15.33	20.50	18.50	15.75	15.75	15.25	12.50	16.00	13.25	16.75	15.50	14.00	16.67
	Tidal Volumes	.507	.540	.502	.516	.698	.442	.468	.425	.467	.513	.488	.477	.483	.482	.497	.476
	O_2 Uptake	.128	.135	.117	.1267	.151	.127	.122	.123	.124	.119	.130	.114	.132	.121	.119	.125
	CO_2 Excretion	.183	.228	.173	.1947	.309	.175	.176	.157	.177	.165	.188	.167	.199	.181	.178	.197

TABLE 4

MINUTE VENTILATION, RESPIRATORY RATE, TIDAL VOLUMES, O_2 UPTAKE AND CO_2 EXCRETION (EXPIRED AIR)

MEASUREMENTS DURING SUCCESSIVE FOUR MINUTE PERIODS BEFORE AND AFTER MORPHINE 16mg/70Kg

Age / Sex / Subject / S.A. / Ht. / Wt.	Measurement	Control Periods 1	2	3	Mean Control Values	Post Drug Periods 1	2	3	4	5	6	7	8	9	10	11	12
32 yrs. M R.M. 1.81 sq.m. 177 cms. 62.0Kg	Minute Ventilation	4.238	4.276	4.250	4.251	4.738	3.750	3.931	3.773	4.071	3.711	4.034	3.740	3.905	3.640	3.729	3.729
	Respiratory Rate	13.50	13.25	14.00	13.58	14.25	13.25	14.00	13.75	15.25	13.75	14.25	13.50	14.00	14.25	13.75	14.25
	Tidal Volumes	.564	.586	.547	.5654	.595	.470	.513	.496	.484	.486	.513	.492	.501	.474	.499	.478
	O_2 Consumption	.136	.137	.134	.1357	.142	.124	.128	.126	.130	.119	.130	.122	.122	.119	.122	.120
	CO_2 Excretion	.219	.224	.217	.220	.248	.170	.194	.189	.199	.186	.201	.189	.194	.184	.187	.187
32 yrs. F I.S. 2.04 sq.m. 182 cms. 84Kg	Minute Ventilation	3.741	3.755	3.796	3.764	3.141	3.250	3.427	3.305	3.250	3.509	3.578	3.250	3.318	3.332	3.400	3.359
	Respiratory Rate	17.00	17.50	18.00	17.50	15.75	16.25	16.50	16.00	16.25	16.25	17.00	17.00	17.50	15.50	16.25	16.00
	Tidal Volumes	.436	.433	.420	.4295	.385	.395	.424	.418	.431	.423	.421	.369	.369	.429	.435	.432
	O_2 Consumption	.093	.093	.092	.0927	.090	.094	.106		.096		.097	.094	.088		.092	.087
	CO_2 Excretion	.158	.150	.152	.1533	.141	.140	.158		.151		.159	.157	.162		.154	.160
47 yrs. M J.N. 1.86 sq.m. 172 cms. 74Kg	Minute Ventilation	4.179	4.119	4.539	4.278	4.239	3.895	3.895	4.075	4.015	3.730	3.715	3.740	3.605	3.620	4.114	4.114
	Respiratory Rate	14.75	15.50	15.50	15.25	16.00	14.25	14.50	12.50	13.50	14.00	13.25	13.75	12.75	12.75	14.50	13.75
	Tidal Volumes	.509	.487	.542	.5123	.493	505	.497	.589	.568	.503	.511	.506	.516	.516	.535	.513
	O_2 Consumption					Analyses Technically Unsatisfactory											
	CO_2 Excretion																
40 yrs. M A.W. 1.89 sq.m. 177 cms. 72.5Kg	Minute Ventilation	4.425	4.630	4.955	4.670	4.852	3.968	4.153	4.332	4.188	4.414	4.291	4.373	4.455	4.373	4.434	4.578
	Respiratory Rate	14.25	13.75	14.75	14.25	15.00	12.25	12.25	12.25	12.00	13.00	12.75	13.50	13.25	13.50	13.50	13.75
	Tidal Volumes	.582	.620	.619	.6067	.605	.615	.647	.672	.622	.614	.643	.618	.635	.642	.627	.625
	O_2 Consumption	.134	.141	.143	.1393	.138	.142	.145	.146	.144	.142	.137	.139	.138	.132	.134	.139
	CO_2 Excretion	.233	.242	.258	.2443	.255	.236	.234	.248	.238	.242	.238	.239	.235	.232	.236	.241
54 yrs. M W.H. 1.76 sq.m. 165 cms. 75.5Kg	Minute Ventilation	5 075	4.998	4.968	5.014	4.860	4.768	4.614	4.676	4.629	4.602	4.476	4.568	4.922	4.506	4.583	4.752
	Respiratory Rate	20.75	20.25	19.50	20.17	21.25	19.50	18.25	18.75	17.75	18.00	17.50	17.75	18.75	17.25	17.25	18.25
	Tidal Volumes	.448	.450	.463	.4533	.419	.444	.459	.459	.474	.591	.469	.472	.476	.476	.482	.478
	O_2 Consumption	.153	.152	.149	.1513	.153	.159	.154	.160	.162	.159	.157	.158	.159	.152	.155	.164
	CO_2 Excretion	.215	.210	.211	.2120	.202	.206	.207	.210	.212	.210	.210	.211	.217	.204	.207	.216
31 yrs M W.D. 1.76 sq.m. 171 cms. 65.35Kg	Minute Ventilation	4.948	5.298	5.234	5.160	5.107	4.225	4.709	5.330	5.250	5.234	5.043	5.091	4.964	5.091	4.725	5.409
	Respiratory Rate	16.75	18.50	18.50	17.92	17.75	16.75	16.75	18.50	19.75	18.75	17.75	18.00	17.75	19.75	17.00	21.75
	Tidal Volumes	.524	.501	.500	.5083	.519	.499	.484	.499	.472	.488	.506	.504	.492	.449	.491	.447
	O_2 Consumption	.147	.149	.152	.1493	.151	.151	.152	.156	.151	.148	.147	.152	.149	.144	.144	.144
	CO_2 Excretion	.209	.221	.216	.2153	.215	.205	.207	.226	.218	.215	.211	.212	.209	.202	.199	.208
32 yrs. M W.J. 1.93 sq.m. 190 cms. 90Kg	Minute Ventilation	4.004	4.303	4.686	4.332	5.123	4.456	3.789	3.306	3.391	3.704	3.278	3.448	3.448	3.576	3.661	3.547
	Respiratory Rate	11.50	12.25	12.25	12.00	13.00	10.00	10.50	10.50	9.00	10.00	12.00	11.75	11.50	9.00	10.00	10.00
	Tidal Volumes	.698	.706	.773	.7344	.791	.830	.722	.575	.743	.772	.540	.556	.556	.804	.715	.703
	O_2 Consumption	.141	.137	.137	.1417	.171	.1905	.1790	.134	.141	.151	.133	.149	.143	.144	.141	.141
	CO_2 Excretion	.328	.257	.251	.2387	.273	.232	.203	.177	.189	.214	.177	.190	.198	.218	.216	.206
30 yrs. M G.F. 1.73 sq.m. 173 cms. 65.5Kg	Minute Ventilation	4.970	5.575	5.591	5.380	5.894	4.699	4.763	4.556	4.970	4.601	5.063	4.649	4.537	4.362	4.330	4.760
	Respiratory Rate	20.25	21.00	23.00	21.42	28.00	21.50	20.75	17.75	18.50	18.00	19.00	18.00	17.25	15.75	16.25	16.50
	Tidal Volumes	.441	.468	.430	.4460	.379	.386	.405	.462	.475	.450	.470	.457	.463	.489	.486	.501
	O_2 Consumption	.157	.174	.167	.1660	.165	.155	.157	.162	.165	.147	.162	.150	.152	.152	.150	.153
	CO_2 Excretion	.228	.253	.253	.2447	.246	.208	.219	.225	.237	.211	.235	.219	.223	.222	.222	.238
49 yrs M A.McK. 1.93 sq.m. 187 cms. 70.1Kg	Minute Ventilation	5.801	5.837	5.937	5.859	5.507	4.846	4.969	5.263	5.356	5.162	5.223	5.616	5.330	5.080	5.230	5.144
	Respiratory Rate	17.50	18.00	18.75	18.08	18.00	15.50	15.25	16.00	16.50	15.00	15.25	16.75	15.50	16.00	15.25	15.00
	Tidal Volumes	.621	.633	.609	.6208	.595	.588	.607	.628	.620	.643	.616	.632	.632	.627	.654	.670
	O_2 Consumption	.145	.149	.146	.1467	.137	.138	.146	.150	.141	.144	.145	.148	.137	.142	.142	.140
	CO_2 Excretion	.239	.239	.239	.239	.216	.195	.214	.220	.222	.222.	.226	.232	.212	.216	.220	.220
60 yrs. M	Minute Ventilation																

MINUTE VENTILATION, RESPIRATORY RATE, TIDAL VOLUMES, O_2 UPTAKE AND CO_2 EXCRETION (EXPIRED AIR)

MEASUREMENTS DURING SUCCESSIVE FOUR MINUTE PERIODS BEFORE AND AFTER MORPHINE 15mg/70Kg

Age / Sex / Subject / S.A. / Ht. / Wt.	Measurement	Contrd Periods 1	2	3	Mean Control Values	Post Drug Periods 1	2	3	4	5	6	7	8	9	10	11	12
45 yrs M	Minute Ventilation	5.181	5.002	5.091	5.092	4.928	4.764	4.571	4.497	4.527	4.527	4.482	4.720	4.312	4.506	4.342	4.178
J.R.	Respiratory Rate	16.50	15.50	16.75	16.25	15.25	15.00	15.25	15.25	15.25	15.00	15.25	16.25	14.25	15.00	14.25	14.00
1.87 sq.m.	Tidal Volumes	.585	.579	.551	.572	.570	.560	.546	.549	.558	.551	.537	.536	.565	.555	.556	.532
178cms. 71.1Kg	O_2 Uptake	.161	.163	.157	.1570	.158	.151	.149	.146	.148	.152	.141	.142	.136	.143	.143	.138
	CO_2 Excretion	.257	.249	.245	.2503	.247	.235	.231	.226	.231	.239	.224	.234	.213	.224	.223	.212
65 yrs. M	Minute Ventilation	4.062	3.926	4.062	4.016	2.839	2.824	3.001	3.303	3.343	3.163	2.997	3.100	3.145	2.844	3.206	3.401
J.P.	Respiratory Rate	12.25	11.33	12.00	11.90	8.25	10.25	10.25	10.00	11.00	10.50	10.33	9.67	10.50	9.25	10.00	10.25
1.85 sq.m.	Tidal Volumes	.579	.621	.596	.598	.563	.504	.531	.583	.538	.572	.552	.598	.571	.573	.602	.609
174 cms. 84.75Kg	O_2 Uptake	.121	.121	.126	.1227	.098	.123	.122	.121	.119	.114	.108	.114	.110	.104	.117	.117
	CO_2 Excretion	.199	.197	.209	.2017	.150	.159	.170	.191	.190	.184	.177	.183	.184	.164	.189	.199
62 yrs F	Minute Ventilation	4.435	4.182	4.456	4.357	3.231	3.206	3.459	3.606	3.585	3.627	3.733	3.712	3.775	3.750	3.919	4.067
C.D.	Respiratory Rate	16.50	15.75	16.33	16.18	13.75	11.67	11.75	12.25	12.67	12.00	13.00	11.67	12.33	13.00	13.75	13.25
1.32 sq.m.	Tidal Volumes	.343	.347	.339	.343	.311	.389	.383	.406	.380	.400	.385	.385	.403	.381	.382	.416
152 cms. 41Kg	O_2 Uptake	.126	.118	.125	.123	.103	.113	.130	.127	.126	.127	.133	.126	.129	.129	.130	.133
	CO_2 Excretion	.133	.128	.134	.1317	.101	.103	.124	.129	.125	.133	.132	.129	.133	.129	.135	.146
62 yrs. M	Minute Ventilation	4.767	4.621	4.704	4.697	3.564	3.619	3.619	3.473	3.523	3.326	3.443	3.619	3.415	3.545	3.823	3.721
W.I.	Respiratory Rate	19.33	18.75	18.75	18.91	17.25	15.25	15.75	14.75	14.75	14.50	14.75	14.50	14.50	13.67	14.25	1500
1.91 sq.m.	Tidal Volumes	.469	.456	.485	.470	.395	.446	.442	.448	.459	.443	.446	.466	.455	.459	.494	.452
175cms. 76.15Kg	O_2 Uptake	.134	.134	.139	.1357	.1227	.134	.130	.121	.122	.117	.117	.125	.118	.122	.129	.124
	CO_2 Excretion	.228	.225	.234	.2290	.175	.185	.189	.183	.184	.179	.182	.191	.183	.191	.204	.195
41 yrs. M	Minute Ventilation	5.291	5.444	5.352	5.363	5.583	4.964	4.826	4.765	4.841	5.025	4.687	4.806	4.714	4.820	4.591	4.760
J.McK.	Respiratory Rate	16.75	17.00	18.50	17.42	18.75	17.00	17.00	16.50	16.25	16.00	16.50	16.50	16.25	16.25	16.00	15.50
1.82 sq.m.	Tidal Volumes	.555	.541	.509	.535	.519	.516	.490	.510	.515	.538	.519	.521	.518	.544	.535	.541
173 cms. 69.95Kg	O_2 Uptake	.160	.150	.145	.1517	.158	.160	.152	.148	.147	.149	.141	.143	.142	.146	.141	.140
	CO_2 Excretion	.217	.212	.207	.2120	.212	.202	.196	.200	.199	.209	.193	.193	.195	.199	.192	.196
65 yrs. M	Minute Ventilation	5.121	5.079	4.906	5.035	5.036	3.911	4.320	4.212	4.298	4.169	4.149	4.127	4.212	3.955	3.653	3.911
A.N.	Respiratory Rate	22.75	22.00	20.75	21.83	19.25	19.00	20.00	21.00	20.50	18.75	17.50	17.75	18.50	16.75	16.75	16.25
1.81 sq.m.	Tidal Volumes	3388	.400	.415	.401	.457	.352	.378	.364	.372	.390	.418	.420	.432	.422	.390	.427
171 cms. 69.5Kg	O_2 Uptake				.1180	.130	.117	.124	.121	.114	.112	.110	.115	.117	.114	.106	.108
	CO_2 Excretion				.1723	.187	.143	.161	.158	.160	.159	.165	.163	.169	.159	.145	.159
42 yrs M	Minute Ventilation	4.179	4.048	4.086	4.104	3.748	3.354	3.599	3.597	3.485	3.711	3.674	3.992	4.086	3.917	3.708	3.764
J.C.	Respiratory Rate	15.00	13.75	13.75	14.17	14.50	14.00	14.50	14.75	13.75	14.75	15.25	15.00	16.00	14.25	13.50	13.75
2.08 sq.m.	Tidal Volumes	.578	.594	.590	.587	.547	.498	.531	.502	.530	.511	.482	1543	.508	.555	.562	.563
186 cms. 84.75Kg	O_2 Uptake	.115	.115	.116	.1153	.114	.118	.123	.115	.114	.119	.114	.119	.118	.117	.117	.116
	CO_2 Excretion	.201	.199	.201	.2003	.189	.176	.188	.181	.182	.191	.186	1200	.195	.197	.195	.197
49yrs. M	Minute Ventilation	4.749	4.292	4.312	4.451	3.982	3.649	3.752	3.793	3.890	3.890	3.889	3.932	3.952	3.993	3.973	4.014
A.M.	Respiratory Rate	21.25	19.00	18.75	19.67	20.50	18.50	18.50	17.75	18.75	19.00	18.00	17.25	17.25	16.75	16.75	17.00
1.89sq.m.	Tidal Volumes	.417	.420	.433	.423	.367	.368	.382	.400	.393	.380	.412	.430	.427	.445	.447	.441
174cms. 74.5Kg	O_2 Uptake	.133	.125	.129	.1290	.119	.130	.133	.132	.131	1128	1133	.132	.133	.135	.133	.136
	CO_2 Excretion	.205	.193	.200	.1993	.171	.174	.184	.191	.194	.190	.194	.199	.201	.208	.203	.208
52yrs. M	Minute Ventilation	4.995	5.009	4.909	4.980	3.553	3.411	3.568	3.967	4.095	4.095	3.796	4.195	4.181	3.881	3.824	4.195
H.S.	Respiratory Rate	19.00	19.75	18.50	19.08	15.75	13.50	14.75	16.00	14.25	15.75	14.25	15.00	15.25	14.00	14.00	14.25
197sq.m.	Tidal Volumes	.517	.504	.527	.516	.452	1545	.489	.522	.562	.538	.516	.551	.544	.542	.542	.579
174cms. 81.5Kg	O_2 Uptake	.131	.127	.128	.1287	.113	.134	.129	.134	.139	.128	.124	.144	.136	.124	.132	.143
	CO_2 Excretion	.222	.221	.217	.2200	.168	.190	.189	.210	.217	.213	.195	.229	.226	.210	.206	.225

TABLE 6

MINUTE VENTILATION, RESPIRATORY RATE, TIDAL VOLUMES, O_2 UPTAKE AND CO_2 EXCRETION (EXPIRED AIR)

MEASUREMENTS DURING SUCCESSIVE FOUR MINUTE PERIODS BEFORE AND AFTER MORPHINE 20mg/70Kg

Age Sex Subject S.A. Ht. Wt.	Measurement	Control Periods			Mean Control Values	Post Drug Periods											
		1	2	3		1	2	3	4	5	6	7	8	9	10	11	12
40 yrs. M W.F. 1.80 sq.m. 173 cms. 67.8Kg	Minute Ventilation	5.730	5.668	5.462	5.630	4.735	4.347	4.657	4.565	4.559	4.617	4.848	4.894	4.909	4.918	4.857	4.841
	Respiratory Rate	22.75	23.25	22.75	22.92	21.00	18.25	19.75	19.50	19.50	20.00	21.00	20.75	21.50	20.50	20.25	20.50
	Tidal Volumes	.440	.434	.436	.4368	.415	.424	.428	.434	.427	.422	.431	.428	.414	.434	.429	.427
	O_2 Uptake	.154	.148	.151	.1510	.142	.147	.152	.147	.147	.148	.149	.151	.146	.144	.143	.137
	CO_2 Excretion	.237	.219	.228	.2280	.197	.195	.206	.205	.209	.207	.210	.213	.209	.206	.205	.204
62 yrs. M C.R. 1.98 sq.m. 167 cms. 90.7Kg	Minute Ventilation	5.009	4.884	4.785	4.871	4.012	4.206	4.221	4.234	4.262	4.172	4.270	4.382	4.410	4.337	4.252	4.364
	Respiratory Rate	18.25	17.75	17.50	17.85	17.50	15.75	15.25	16.25	16.50	17.00	17.00	17.00	17.00	17.25	16.25	16.50
	Tidal Volumes	.522	.543	.544	.5363	.436	.522	.510	.487	.498	.485	.459	.489	.497	.492	.501	.529
	O_2 Uptake	.150	.145	.149	.1480	.125	.162	.164	.159	.157	.153	.153	.155	.153	.149	.150	.150
	CO_2 Excretion	.238	.228	.230	.2320	.178	.212	.222	.220	.218	.218	.220	.228	.230	.228	.224	.230
42 yrs. M J.R. 1.80 sq.m. 171 cms. 68.5Kg	Minute Ventilation	4.695	4.587	4.968	4.745	3.730	3.235	3.358	3.544	3.606	3.714	3.807	3.885	3.838	3.761	3.699	3.636
	Respiratory Rate	15.50	16.00	15.25	15.58	14.00	12.00	12.00	13.00	12.25	13.75	13.00	13.25	13.25	13.75	13.50	12.67
	Tidal Volumes	.546	.525	.595	.5550	.463	.485	.514	.512	.537	.488	.529	.532	.519	.511	.518	.519
	O_2 Uptake	.144	.136	.151	.1437	.119	.135	.141	.140	.137		.138		.142	.141	.141	.132
	CO_2 Excretion	.214	.205	.235	.2180	.176	.164	.183	.189	.190		.198		.194	.191	.193	.193
53 yrs. M J.D. 1.76 sq.m. 170 cms. 66.8Kg	Minute Ventilation	5.457	5.457	5.695	5.547	4.881	4.770	5.047	5.094	5.110	4.888	4.778	4.960	5.213	5.213	5.150	5.007
	Respiratory Rate	14.75	14.75	15.25	14.92	15.25	14.25	14.50	15.00	15.00	14.75	14.25	14.50	15.50	15.00	14.50	14.50
	Tidal Volumes	.652	.647	.656	.6516	.575	.589	.614	.613	.599	.585	.580	.598	.590	.617	.624	.621
	O_2 Uptake	.143	.140	.144	.1423	.134	.150	.152	.149	.147	.141	.139	.141	.146	.149	.144	.140
	CO_2 Excretion	.209	.205	.213	.2090	.181	.189	.207	.210	.209	.200	.192	.203	.210	.216	.214	.202

TABLE 7

CHANGES IN MINUTE VENTILATION, RESPIRATORY RATE, TIDAL VOLUMES, O_2 UPTAKE AND CO_2 EXCRETION AFTER 5mg/70Kg MORPHINE

	Minute Ventilation L/m^2 B.T.P.S.					Respiratory Rate Breaths/min.					Tidal Volumes L. B.T.P.S.					O_2 Uptake L/min./m^2 S.T.P.D.				
NAME	CONTROL	POST DRUG	CHANGE	't' VALUE	DEGREES OF FREEDOM	CONTROL	POST DRUG	CHANGE	't' VALUE	DEGREES OF FREEDOM	CONTROL	POST DRUG	CHANGE	't' VALUE	DEGREES OF FREEDOM	CONTROL	POST DRUG	CHANGE	't' VALUE	DEGREES OF FREEDOM
W.B.	4.688 ± .124 (.7306)	4.353 ± .113 (.7801)	-.335	1.977 (1)	32	13.50 ± .48 (1.68)	13.75 ± .30 (2.10)	+0.25	.382	58	.5804 ± .0182 (.0630)	.5266 ± .0137 (.0950)	-.0538	1.855	58	.1427 ± .0043 (.0075)	.1406 ± .0022 (.0074)	-.0021	.438	12
G.R.	4.209 ± .1011 (.3501)	4.021 ± .0417 (.2890)	-.188	1.932 (1)	58	16.25 ± .87 (.06)	14.90 ± .18 (1.26)	-1.35	3.517 ****	58	.4723 ± .0096 (.0334)	.4975 ± .0045 (.0308)	+.0252	2.495 **	58	.1413 ± .0009 (.0016)	.1397 ± .0016 (.0054)	-.0016	.500	13
W.E.	4.487 ± .0540 (.1871)	4.058 ± .0237 (.1641)	-.429	7.872 ****	58	15.33 ± .31 (1.07)	15.48 ± .10 (.68)	+.15	.602	58	.5428 ± .0069 (.0237)	.4875 ± .0033 (.0230)	-.0553	7.393 ****	58	.1310 ± .0011 (.0020)	.1254 ± .0012 (.0043)	-.0056	2.154 *	13
J.H.	3.621 ± .1313 (.4550)	3.389 ± .0483 (.3347)	-.232	2.000 *	58	12.42 ± .61 (2.11)	12.13 ± .38 (2.60)	-.29	.360	58	.5178 ± .0166 (.0575)	.5091 ± .0172 (.1190)	-.0087	.245	58					
F.G.	3.931 ± .0831 (.2877)	3.955 ± .0450 (.3116)	+.024	.242	58	12.92 ± .45 (1.56)	15.38 ± .24 (1.63)	+2.46	4.704 ****	58	.5872 ± .0162 (.0560)	.4970 ± .0048 (.0329)	-.0902	7.260 ****	57	.1400 ± .0017 (.0030)	.1332 ± .0010 (.0036)	-.0068	3.022 ****	13
M.W.	4.326 ± .2531 (.8767)	4.377 ± .2158 (1.4946)	+.051	.113	58	15.33 ± .58 (2.02)	15.85 ± .40 (2.76)	+.52	.609	57	.5163 ± .0180 (.0622)	.4928 ± .0143 (.0988)	-.0235	.783	58	.1267 ± .0051 (.0091)	.1256 ± .0027 (.0094)	-.0011	.183	13

(1) Just short of 5% level of significance

* significant change $.05 > p > .02$
** significant change $.02 > p > .01$
*** significant change $.01 > p > .001$
**** significant change $p < .001$

Other 't' values are not significant at 5% level.

TABLE 7

CHANGES IN MINUTE VENTILATION, RESPIRATORY RATE, TIDAL VOLUMES, O_2 UPTAKE AND CO_2 EXCRETION AFTER 5mg/70Kg MORPHINE

Respiratory Rate Breaths/min.					Tidal Volumes L. B.T.P.S.					O_2 Uptake L/min./m^2 S.T.P.D.					CO_2 Excretion L/min. S.T.P.D.				
CONTROL	POST DRUG	CHANGE	't' VALUE	DEGREES OF FREEDOM	CONTROL	POST DRUG	CHANGE	't' VALUE	DEGREES OF FREEDOM	CONTROL	POST DRUG	CHANGE	't' VALUE	DEGREES OF FREEDOM	CONTROL	POST DRUG	CHANGE	't' VALUE	DEGREES OF FREEDOM
13.50 ± .48 (1.68)	13.75 ± .30 (2.10)	+0.25	.382	58	.5804 ± .0182 (.0630)	.5266 ± .0137 (.0950)	-.0538	1.855	58	.1427 ± .0043 (.0075)	.1406 ± .0022 (.0074)	-.0021	.438	12	.2053 ± .0054 (.0093)	.1864 ± .0065 (.0224)	-.0189	1.400	13
16.25 ± .87 (.06)	14.90 ± .18 (1.26)	-1.35	3.517****	58	.4723 ± .0096 (.0334)	.4975 ± .0045 (.0308)	+.0252	2.495**	58	.1413 ± .0009 (.0016)	.1397 ± .0016 (.0054)	-.0016	.500	13	.2073 ± .002 (.0035)	.2096 ± .0040 (.0140)	+.0023	.274	13
15.33 ± .31 (1.07)	15.48 ± .10 (.68)	+.15	.602	58	.5428 ± .0069 (.0237)	.4875 ± .0033 (.0230)	-.0553	7.393****	58	.1310 ± .0011 (.0020)	.1254 ± .0012 (.0043)	-.0056	2.154*	13	.2163 ± .0027 (.0047)	.1935 ± .0014 (.0049)	-.0228	7.284****	13
12.42 ± .61 (2.11)	12.13 ± .38 (2.60)	-.29	.360	58	.5178 ± .0166 (.0575)	.5091 ± .0172 (.1190)	-.0087	.245	58										
12.92 ± .45 (1.56)	15.38 ± .24 (1.63)	+2.46	4.704****	58	.5872 ± .0162 (.0560)	.4970 ± .0048 (.0329)	-.0902	7.260****	57	.1400 ± .0017 (.0030)	.1332 ± .0010 (.0036)	-.0068	3.022****	13	.2250 ± .0023 (.0040)	.2121 ± .0018 (.0063)	-.0129	3.316****	13
15.33 ± .58 (2.02)	15.85 ± .40 (2.76)	+.52	.609	57	.5163 ± .0180 (.0622)	.4928 ± .0143 (.0988)	-.0235	.783	58	.1267 ± .0051 (.0091)	.1256 ± .0027 (.0094)	-.0011	.183	13	.1947 ± .0169 (.0293)	.1891 ± .0115 (.0397)	-.0056	.227	13

(1) Just short of 5% level of significance

* significant change .05 > p > .02
** significant change .02 > p > .01
*** significant change .01 > p > .001
**** significant change p < .001

Other 't' values are not significant at 5% level.

TABLE 8

CHANGES IN MINUTE VENTILATION, RESPIRATORY RATE, TIDAL VOLUMES, O_2 UPTAKE AND CO_2 EXCRETION AFTER 10mg/70Kg MORPHINE

		MINUTE VENTILATION				RESPIRATORY RATE					TIDAL VOLUMES					O_2 UPTAKE				
NAME	CONTROL	POST DRUG	CHANGE	't' VALUE	DEGREES OF FREEDOM	CONTROL	POST DRUG	CHANGE	't' VALUE	DEGREES OF FREEDOM	CONTROL	POST DRUG	CHANGE	't' VALUE	DEGREES OF FREEDOM	CONTROL	POST DRUG	CHANGE	't' VALUE	DEGREES OF FREEDOM
R.M.	4.251±.0660 (.2285)	3.862±.0555 (.4298)	-.389	3.039	70	13.58±.26 (.90)	14.07±.13 (.97)	+.48	1.592	70	.5654±.0091 (.0315)	.4964±.0018 (.0434)	-.0690	5.227	70	.1357±.0009 (.0016)	.1246±.0017 (.0067)	-.0111	2.777	16
I.S.	3.764±.0477 (.1654)	3.343±.0233 (.1616)	-.421	8.034	58	17.50±.29 (1.00)	16.34±.14 (.984)	-1.16	3.636	58	.4195±.0042 (.0144)	.4109±.0051 (.0356)	-.0186	2 810	45	.0927±.0004 (.0007)	.0938±.0019 (.0057)	+.0011	.323	10
J.N.	4.278±.0829 (.2872)	3.904±.0522 (.3677)	-.374	3.324	58	15.25±.28 (.96)	13.79±.20 (1.37)	-1.46	3.471	58	.5123±.0128 (.0445)	.5209±.0078 (.0541)	+.0086	.509	58					
W.J.	4.332±.1459 (.5054)	3.727±.0863 (.5977)	-.605	3.223	58	12.00±.35 (1.21)	10.60±.24 (1.65)	-1.40	2.748	58	.7244±.0219 (.0759)	.6908±.0180 (.1247)	-.0336	1.185	28	.1477±.0033 (.0058)	.1449±.0029 (.0101)	-.0028	.453	13
G.F.	5.380±.2043 (.7078)	4.765±.0738 (.5116)	-.615	3.438	58	21.42±.40 (1.38)	18.94±.49 (3.38)	-2.48	2.477	58	.4460±.0144 (.0497)	.4507±.0069 (.0476)	+.0047	.303	57	.1660±.0049 (.0085)	.1558±.0018 (.0063)	-.0102	2.373	13
A.W.	4.670±.1966 (.6812)	4.368±.0759 (.5258)	-.302	1.678	58	14.25±.33 (1.14)	13.08±.19 (1.35)	-1.17	2.752	58	.6067±.0146 (.0507)	.6303±.0063 (.0434)	+.0236	1.628	58	.1393±.0027 (.0047)	.1397±.0012 (.0043)	+.0004	.142	13
W.H.	5.014±.0574 (.1987)	4.662±.0367 (.2569)	-.352	4.422	59	20.17±.27 (.94)	18.35±.193 (1.35)	-1.82	4.417	59	.4533±.0054 (.0186)	.4650±.0031 (.0219)	+.0117	1.706	59	11513±.0012 (.0021)	.1577±.0011 (.0031)	+.0064	2.870	13
W.D.	5.160±.0912 (.3158)	5.053±.0593 (.4106)	-.107	.843	58	17.92±.36 (1.24)	18.35±.27 (1.84)	+0.43	.782	58	.5083±.0071 (.0244)	.4872±.0054 (.0374)	-.0211	1.851	58	.1493±.0015 (.0026)	.1491±.0011 (.0038)	-.0002	.085	13
A.M.	5.859±.0837 (.2899)	5.228±.0764 (.5292)	-.631	3.968	58	18.08±.40 (1.38)	15.83±.23 (1.57)	-2.25	4.527	58	.6208±.0070 (.0241)	.6261±.0072 (.0498)	+.0053	.529	37	.1467±.0012 (.0021)	.1425±.0012 (.0042)	-.0042	1.634	13

TABLE 8

CHANGES IN MINUTE VENTILATION, RESPIRATORY RATE, TIDAL VOLUMES, O_2 UPTAKE AND CO_2 EXCRETION AFTER 10mg/70Kg MORPHINE

RESPIRATORY RATE					TIDAL VOLUMES					O_2 UPTAKE					CO_2 EXCRETION				
CONTROL	POST DRUG	CHANGE	't' VALUE	DEGREES OF FREEDOM	CONTROL	POST DRUG	CHANGE	't' VALUE	DEGREES OF FREEDOM	CONTROL	POST DRUG	CHANGE	't' VALUE	DEGREES OF FREEDOM	CONTROL	POST DRUG	CHANGE	't' VALUE	DEGREES OF FREEDOM
13.58±.26 (.90)	14.07±.13 (.97)	+.48	1.592	70	.5654±.0091 (.0315)	.4964±.0018 (.0434)	-.0690	5.227	70	.1357±.0009 (.0016)	.1246±.0017 (.0067)	-.0111	2.777	16	.2200±.002 (.036)	.1941±.0055 (.0190)	-.0269	2.450	16
17.50±.29 (1.00)	16.34±.14 (.984)	-1.16	3.636	58	.4195±.0042 (.0144)	.4109±.0051 (.0356)	-.0186	2 810	45	.0927±.0004 (.0007)	.0938±.0019 (.0057)	+.0011	.323	10	.1533±.0024 (.0042)	.1536±.0027 (.0080)	+.003	.622	10
15.25±.28 (.96)	13.79±.20 (1.37)	-1.46	3.471	58	.5123±.0128 (.0445)	.5209±.0078 (.0541)	+.0086	.509	58										
12.00±.35 (1.21)	10.60±.24 (1.65)	-1.40	2.748	58	.7244±.0219 (.0759)	.6908±.6180 (.1247)	-.0336	1.185	28	.1477±.0033 (.0058)	.1449±.0029 (.0101)	-.0028	.453	13	.2387±.0067 (.0116)	.2077±.0076 (.0265)	-.0310	1.938	13
21.42±.40 (1.38)	18.94±.49 (3.38)	-2.48	2.477	58	.4460±.0144 (.0497)	.4507±.0069 (.0476)	+.0047	.303	57	.1660±.0049 (.0085)	.1558±.0018 (.0063)	-.0102	2.373	13	.2447±.0083 (.0144)	.2254±.0033 (.0114)	-.0193	2.510	13
14.25±.33 (1.14)	13.08±.19 (1.35)	-1.17	2.752	58	.6067±.6146 (.0507)	.6303±.0063 (.0434)	+.0236	1.628	58	.1393±.0027 (.0047)	.1397±.0012 (.0043)	+.0004	.142	13	.2443±.0073 (.0126)	.2387±.0021 (.0075)	-.0056	1.020	13
20.17±.27 (.94)	18.35±.193 (1.35)	-1.82	4.417	59	.4533±.0054 (.0186)	.4650±.0031 (.0219)	+.0117	1.706	59	11513±.0012 (.0021)	.1577±.0011 (.0031)	+.0064	2.870	13	.2120±.0015 (.0026)	.2093±.0013 (.0045)	-.0027	.989	13
17.92±.36 (1.24)	18.35±.27 (1.84)	+0.43	.782	58	.5083±.0071 (.0244)	.4872±.0054 (.0374)	-.0211	1.851	58	.1493±.0015 (.0026)	.1491±.0011 (.0038)	-.0002	.085	13	.2153±.0034 (.0060)	.2106±.0021 (.0074)	-.0047	1.016	13
18.08±.40 (1.38)	15.83±.23 (1.57)	-2.25	4.527	58	.6208±.0070 (.0241)	.6261±.0072 (.0498)	+.0053	.529	37	.1467±.0012 (.0021)	.1435±.0012 (.0042)	-.0042	1.634	13	.2390± 0 (	.2179±.0026 (.0090)	-.0211	3.944	13

TABLE 9

CHANGES IN MINUTE VENTILATION, RESPIRATORY RATE, TIDAL VOLUMES, O_2 UPTAKE AND CO_2 EXCRETION AFTER 5mg/70Kg MORPHINE

	Minute Ventilation L/M^2 BTPS					Respiratory Rate - Breaths/Min.					Tidal Volume L BTPS					O_2 Uptake L/M^2/min. STPD					CO_2 Excretion L/Min. STPD				
NAME	CONTROL	POST DRUG	CHANGE	't' VALUE	DEGREES OF FREEDOM	CONTROL	POST DRUG	CHANGE	't' VALUE	DEGREES OF FREEDOM	CONTROL	POST DRUG	CHANGE	't' VALUE	DEGREES OF FREEDOM	CONTROL	POST DRUG	CHANGE	't' VALUE	DEGREES OF FREEDOM	CONTROL	POST DRUG	CHANGE	't' VALUE	DEGREES OF FREEDOM
J.R.	5.092±.0065	4.530±.0420	-.562	6.210	58	16.25±.31	15.00±.16	-1.25	3.469	58	.5717±.0107	.5512±.0038	-.0205	2.200	58	.1570±.0035	.1456±.0018	-.0114	2.815	13	.2053±.0035	.2283±.0029	-.022	3.548	13
J.P.	4.016±.1429	3.097±.0538	-.919	7.124	58	11.90±.43	10.02±.16	-1.88	4.803	54	.5983±.0255	.5663±.0105	-.032	1.306	58	.1227±.0017	.1139±.0022	-.0088	1.913	13	.2017±.0037	.1783±.0042	-.0234	2.647	13
C.D.	4.357±.0753	3.649±.0486	-.708	6.834	57	16.18±.30	12.71±.15	-3.47	10.321	51	.3426±.0034	.3850±.0054	+.0424	3.855	58	.1230±.0025	.1255±.0025	+.0025	.472	13	.1317±.0019	.1266±.0037	-.0051	.671	13
W.I.	4.697±.0490	3.558±.0342	-1.139	15.646	58	18.91±.44	14.94±.178	-3.97	9.370	56	.4697±.0063	.4503±.0042	-.0194	2.153	58	.1357±.0017	.1234±.0015	-.0123	3.785	13	.2290±.0027	.1868±.0023	-.0422	8.866	13
J.McK.	5.363±.0698	4.865±.0469	-.498	49.602	58	17.42±.40	16.54±.14	-.825	2.53	58	.5351±.0089	.5221±.0034	-.013	-1.615	58	.1517±.0044	.1473±.0019	-.0044	1.00	13	.2120±.0029	.1988±.0018	-.0132	3.350	13
A.N.	5.035±.0524	4.163±.0588	-.872	7.207	58	21.83±.41	18.50±.25	-3.33	6.253	56	.4008±.0056	.4016±.0061	+.0008	.084	58	.1180±.0013	.1157±.0020	-.0023	.780	16	.1723±.0029	.1607±.0032	-.0116	2.315	16
J.C.	4.104±.0612	3.721±.0454	-.383	3.985	58	14.17±.24	14.50±.14	+.33	1.114	58	.5869±.0051	.5275±.0062	-.0594	4.677	58	.1153±.0004	.1170±.0008	+.0017	1.069	13	.2003±.0002	.1898±.0022	-.0105	2.370	13
A.M.	4.451±.0899	3.889±.0349	-.562	6.787	58	19.67±.51	18.00±.23	-1.67	3.163	58	.4231±.0073	.4076±.0055	-.0155	1.348	58	.1290±.0023	.1313±.0013	+.0023	.821	13	.1993±.0035	.1931±.0035	-.0062	.850	13
H.S.	4.980±.0852	3.896±.0710	-1.084	7.285	58	19.08±.36	14.73±.22	-4.35	9.205	58	.5158±.0132	.5318±.0091	+.016	.825	58	.1287±.0012	.1317±.0025	+.003	.571	13	.220±.0015	.2065±.0052	-.0135	1.250	13

TABLE 9

CHANGES IN MINUTE VENTILATION, RESPIRATOR

O_2 UPTAKE AND CO_2 EXCRETION AFTER

	Minute Ventilation L/M^2 BTPS					Respiratory Rate - Breaths/Min.					Tidal Volume L BTPS				
NAME	CONTROL	POST DRUG	CHANGE	't' VALUE	DEGREES OF FREEDOM	CONTROL	POST DRUG	CHANGE	't' VALUE	DEGREES OF FREEDOM	CONTROL	POST DRUG	CHANGE	't' VALUE	DEGRE FREE
J.R.	5.092±.0065	4.530±.0420	-.562	6.210	58	16.25±.31	15.00±.16	-1.25	3.469	58	.5717±.0107	.5512±.0038	-.0205	2.200	58
J.P.	4.016±.1429	3.097±.0538	-.919	7.124	58	11.90±.43	10.02±.16	-1.88	4.803	54	.5983±.0255	.5663±.0105	-.032	1.306	58
C.D.	4.357±.0753	3.649±.0486	-.708	6.834	57	16.18±.30	12.71±.15	-3.47	10.321	51	.3426±.0034	.3850±.0054	+.0424	3.855	58
W.I.	4.697±.0490	3.558±.0342	-1.139	15.646	58	18.91±.44	14.94±.178	-3.97	9.370	56	.4697±.0063	.4503±.0042	-.0194	2.153	58
J.McK.	5.363±.0698	4.865±.0469	-.498	49.602	58	17.42±.40	16.54±.14	-.825	2.53	58	.5351±.0089	.5221±.0034	-.013	-1.615	58
A.N.	5.035±.0524	4.163±.0588	-.872	7.207	58	21.83±.41	18.50±.25	-3.33	6.253	56	.4008±.0056	.4016±.0061	+.0008	.064	58
J.C.	4.104±.0612	3.721±.0454	-.383	3.985	58	14.17±.24	14.50±.14	+.33	1.114	58	.5869±.0051	.5275±.0062	-.0594	4.677	58
A.M.	4.451±.0899	3.889±.0349	-.562	6.787	58	19.67±.51	18.00±.23	-1.67	3.163	58	.4231±.0073	.4076±.0055	-.0155	1.348	58
H.S.	4.980±.0852	3.896±.0710	-1.084	7.285	58	19.08±.36	14.73±.22	-4.35	9.205	58	.5158±.0132	.5318±.0091	+.016	.825	58

Y RATE, TIDAL VOLUMES,

Omg/70Kg MORPHINE

	O_2 Uptake L/M^3/min. STPD					CO_2 Excretion L/Min. STPD				
	CONTROL	POST DRUG	CHANGE	't' VALUE	DEGREES OF FREEDOM	CONTROL	POST DRUG	CHANGE	't' VALUE	DEGREES OF FREEDOM
	.1570±.0035	.1486±.0018	-.0114	2.815	13	.2053±.0035	.2283±.0029	-.022	3.548	13
	.1227±.0017	.1139±.0022	-.0088	1.913	13	.2017±.0037	.1783±.0042	-.0234	2.647	13
	.1230±.0028	.1255±.0028	+.0025	.472	13	.1317±.0019	.1266±.0037	-.0051	.671	13
	.1357±.0017	.1234±.0018	-.0123	3.785	13	.2290±.0027	.1868±.0023	-.0422	8.866	13
	.1516±.0044	.1473±.0019	-.0044	1.00	13	.2120±.0029	.1988±.0018	-.0133	3.350	13
	.1190±.0013	.1132±.0020	-.0058	.780	16	.1723±.0029	.1607±.0032	-.0116	2.315	16
	.1153±.0004	.1176±.0008	+.0017	1.069	13	.2003±.0002	.1898±.0022	+.0105	2.370	13
	.1290±.0028	.1313±.0013	+.0023	.821	13	.1903±.0035	.1931±.0035	-.0028	.810	13
	.1287±.0042	.1317±.0028	+.003	.571	13	.220±.0018	.2065±.0052	-.0135	1.210	13

TABLE 10

CHANGES IN MINUTE VENTILATION, RESPIRATORY RATE, TIDAL VOLUMES, O_2 UPTAKE AND CO_2 EXCRETION AFTER 20mg/70Kg MORPHINE

	Minute Ventilation L/M^2 BTPS					Respiratory Rate - Breaths/Min.					Tidal Volume L BTPS					O_2 Uptake L/M^2 STPD				
NAME	CONTROL	POST DRUG	CHANGE	't' VALUE	DEGREES OF FREEDOM	CONTROL	POST DRUG	CHANGE	't' VALUE	DEGREES OF FREEDOM	CONTROL	POST DRUG	CHANGE	't' VALUE	DEGREES OF FREEDOM	CONTROL	POST DRUG	CHANGE	't' VALUE	DEGREES OF FREEDOM
W.F.	5.630±.0722 (.2500)	4.740±.0422 (.2923)	-.890	9.684	58	22.917±.288 (.996)	20.208±.181 (1.254)	-2.709	6.946	58	.4368±.0032 (.0110)	.4259±.0018 (.0126)	-.0109	2.739	58	.151±.00173 (.003)	.1461±.00119 (.0041)	-.0049	1.914	13
C.R.	4.871±.0844 (.2924)	4.241±.0342 (.2367)	-.630	7.855	58	17.833±.297 (1.030)	16.604±.142 (.984)	-1.229	3.036	58	.5363±.0128 (.0442)	.4919±.0049 (.0337)	-.0444	3.828	58	.1480±.00153 (.0026)	.1525±.00285 (.0099)	+.0045	.763	13
J.R.	4.745±.1012 (.3507)	3.650±.0563 (.3901)	-1.095	8.859	58	15.583±.260 (.900)	13.043±.146 (.999)	-2.54	8.013	57	.555±.0123 (.0425)	.5104±.00631 (.0437)	-.0446	3.186	58	.1437±.00434 (.0075)	.1367±.00217 (.0069)	-.007	1.518	11
J.D.	5.547±.0738 (.2558)	5.014±.0382 (.2646)	-.533	6.278	58	14.917±.193 (.669)	14.750±.087 (601)	-.167	.843	58	.6516±.0045 (.0154)	.6003±.0031 (.0214)	-.0513	7.796	58	.1423±.00123 (.0021)	.1443±.00156 (.0054)	+.002	.615	13

TABLE 10

CHANGES IN MINUTE VENTILATION, RESPIRATORY RATE, TIDAL VOLUMES, O_2 UPTAKE AND CO_2 EXCRETION AFTER 20mg/70Kg MORPHINE

Respiratory Rate - Breaths/Min.					Tidal Volume L BTPS					O_2 Uptake L/M^2 STPD					CO_2 Excretion L/Min. STPD				
CONTROL	POST DRUG	CHANGE	't' VALUE	DEGREES OF FREEDOM	CONTROL	POST DRUG	CHANGE	't' VALUE	DEGREES OF FREEDOM	CONTROL	POST DRUG	CHANGE	't' VALUE	DEGREES OF FREEDOM	CONTROL	POST DRUG	CHANGE	't' VALUE	DEGREES OF FREEDOM
22.917±.288 (.996)	20.208±.181 (1.254)	-2.709	6.946	58	.4368±.0032 (.0110)	.4259±.0018 (.0126)	-.0109	2.739	58	.151±.00173 (.003)	.1461±.00119 (.0041)	-.0049	1.914	13	.2280±.0052 (.009)	.2055±.00148 (.00513)	-.0225	6.356	15
17.833±.297 (1.030)	16.604±.142 (.984)	-1.229	3.036	58	.5363±.0128 (.0442)	.4919±.0049 (.0337)	-.0444	3.828	58	.1480±.00153 (.0026)	.1525±.00285 (.0099)	+.0045	.763	13	.2320±.00305 (.0053)	.2190±.00406 (.0141)	-.013	1.548	13
15.583±.260 (.900)	13.043±.146 (.999)	-2.54	8.013	57	.555±.0123 (.0425)	.5104±.00631 (.0437)	-.0446	3.186	58	.1437±.00434 (.0075)	.1367±.00217 (.0069)	-.007	1.518	11	.2180±.00889 (.0154)	.1871±.00323 (.0102)	-.0309	4.142	11
14.917±.193 (.669)	14.750±.087 (601)	-.167	.843	58	.6516±.0045 (.0154)	.6003±.0031 (.0214)	-.0513	7.796	58	.1423±.00123 (.0021)	.1443±.00156 (.0054)	+.002	.615	13	.2090±.00231 (.004)	.2028±.00308 (.0107)	-.0062	.967	13

Table 11

Fractional Changes in Respiration, Oxygen consumption, and carbon dioxide output after morphine, in normal subjects and subjects in left ventricular failure

Treatment Group	CHANGES IN RESPIRATION				CHANGES IN RESPIRATORY EXCHANGE		
	No. of subjects	Minute Ventilation	Respiratory Frequency	Tidal volume	No. of subjects	Oxygen consumption	Carbon dioxide output
5 mg/70 kg	6	-.0423 ± .0177* (.0434)	.0243 ± .0373 (.0914)	-.0595 ± .0298 (.0728)	5	-.0252 ± .0084* (.0189)	-.0545 ± .0224* (.0502)
10 mg/70 kg	9	-.0898 ± .0116**** (.0348)	-.0701 ± .0199 (.0597)	-.0170 ± .017 (.0509)	8	-.0185 ± .0153 (.0434)	-.0583 ± .0176** (.0497)
15 mg/70 kg	9	-.1611 ± .0195**** (.0584)	-.1281 ± .0287 (.0862)	-.0151 ± .0212 (.0635)	9	-.0230 ± .0152 (.0455)	-.0803 ± .0157**** (.0472)
20 mg/70 kg	4	-.1536 ± .0287** (.0574)	-.0903 ± .0326 (.0652)	-.0667 ± .0139** (.0279)	4	-.0092 ± .0187 (.0375)	-.0815 ± .0246* (.0492)
Test for difference between treatment means (F value)		8.754 (3,24) P < .001	4.789 (3,24) .01 > P > .001	1.364 (3,24) P > .2		(1) 6.843 (22,3)	(1) 1.909 (22,3)
Pooled data (where justified by lack of evidence of significant heterogeneity)			(2) -.0975 ± .0159**** (.0744)	(3) -.0326 ± .0113*** (.0596)		(3) 1.0199 ± .0074** (.0380)	(3) -.0687 ± .0093 (.0474)
Left ventricular failure 15 mg/70 kg	6	-.2437 ± .0144*** (.1007)	-.1868 ± .0661* (.1619)	-.0520 ± .0897 (.2197)	6	-.0821 ± .0142*** (.0347)	-.1449 ± .0389** (.0953)

(1) Variance within is greater than between groups

(2) 10, 15 and 20 mg/70 kg groups pooled.

(3) All treatment groups pooled.

Table 12

Fractional changes in minute ventilation during first 4 minutes after morphine (normal subjects and patients in left ventricular failure

Treatment Group	No of Observations	Fractional changes during periods specified Mean ± S.E. (S.D.)			
		1	1,- 2	1, - 3	1, - 4
5 mg /70 kg normals	6	.3306 ± .2190 (.5364)	.3009 ± .2316 (.5672)	.1954 ± .1932 (.4733)	.1230 ± .1522 (.3730)
10 mg/70 kg normals	8	.1202 ± .0697 (.1972)	.0672 ± .0492 (.1392)	.0217 ± .0375 (.1059)	.0052 ± .0368 (.1041)
15 mg/70 kg normals	9	-.0205 ± .0407 (.1221)	-.0846 ± .0469 (.1406)	-.1133 ± .0459* (.1377)	-.1403 ± .0437** (.1310)
20 mg/70 kg normals	4	-.1045 ± .0300* (.0599)	-.1097 ± .0323* (.0646)	-.1465 ± .0201*** (.0401)	-.1683 ± .0204*** (.0409)
Combined 5 and 10 mg/ 70 kg groups normals	14	(1) .2104 ± .1012 (.3785)	.1673 ± .1030 (.3855)	.0962 ± .0846 (.3165)	.0557 ± .0707 (.2510)
Left ventricular failure 15 mg/70 kg	5	(1) .2509 ± .0909 (.2032)	.1768 ± .1637 (.3662)	.0399 ± .1176 (.2631)	.0454 ± .0934 (.2087)

(1) Change just short of significance at .05 level.

TABLE 13

Regression statistics Changes in Minute Ventilation related to Age of Subject

Treatment Group	r	Degrees[1] of Freedom	Syx [2]	(b ± S.E.)[3]
5 mg/70 kg	-.0701	4	.0485	- .000273 ± .00195
10 mg/70 kg	.133	7	.0369	.000504 ± .00141
15 mg/70 kg	-.803	7	.0373	-.00471 ± 00132
20 mg/70 kg	.640	2	.0541	.00358 ± .00304
Common Regression - All groups				
	-.209	23	.0484	-.00101 ± .00099[4]
" "				
5, 10 and 20 mg/ 70 kg groups	.190	16	.0432	.000805 ± .001074

(1) Of the regression constant b

(2) Standard deviation from regression

(3) Slope of regression line with attached standard error

(4) Slopes not homogenous .05 > P > .025

Table 14

Fractional changes in tidal volume during initial four periods following drug administration (25th to 44th minute of standard protocol)

Treatment Group	No. of Subjects	FRACTIONAL CHANGES IN TIDAL VOLUME			
		25 - 29'	25 - 34'	25 - 39'	25 - 44'
5 MG /70 kg	6	.0862 ± .0825 (.2020)	.0577 ± .0681 (.1667)	.0139 ± .0494 (.1810)	-.0105 ± .0406 (.0994)
10 mg/70 kg	8	-.0372 ± .0267 (.0755)	-.0297 ± .0273 (.0774)	-.0246 ± .0102 (.0601)	-.0161 ± .0146 (.0413)
15 mg/70 kg	9	-.0586 ± .0299 (.0897)	-.0549 ± .0193* (.0578)	-.0551 ± .0190** (.0569)	-.0483 ± .0201* (.0604)
20 mg/70 kg	4	-.1301 ± .0304* (.0608)	1.0995 ± .0223* (.0446)	-.0836 ± .0184** (.0367)	-.0769 ± .0176* (.0353)
Test for difference between treatment means		(1) 3.093 (3,23)	2.548 (3,23)	1.690 (3.23)	1.225 (3,23)
F values		P = .05	.1 > P > .05	P = .2	P > .2

(1) F = 1.829 (2,18)
(.2 > P > .1) if
5 mg/70 kg group
is excluded.

TABLE 15

O_2 Uptake / Ventilation
Control and Post Drug Regressions - Normal Subjects - Derived by Covariance Analysis

Treatment Group	Period	Degrees of Freedom	r	S_{yx}	$\bar{y}$	a + (b ± S.E.)	$\bar{x}$	Control - Post Drug Adjusted Means ± S.E.
5 mg/70 kg (5 subjects)	Control	19	.558	.0046	.137	.0998 + (.0088 ± .0030)	4.252	.0042 ± .0011 ****
	Post Drug	38	.644	.0035	.131	.0868 + (.0109 ± .0021)	4.074	
10 mg/70 kg (8 subjects)	Control	34	.720	.0054	.140	.0566 + (.0175 ± .0030)	4.746	-.0056 ± .0013 ****
	Post Drug	63	.535	.0042	.139	.0729 + (.0151 ± .0030)	4.355	
15 mg/70 kg (9 subjects)	Control	36	.706	.0046	.130	.0073 + (.0264 ± .0044)(1)	4.645	-.0131 ± .0017 ****
	Post Drug	72	.705	.0031	.127	.0500 + (.0196 ± .0023)	3.943	
20 mg/70 kg (4 subjects)	Control	15	.677	.0032	.137	.0539 + (.0178 ± .0050)	4.684	-.0020 ± .0036
	Post Drug	29	.218	.0036	.138	.1176 + (.0063 ± .0052)(2)	4.260	
All groups	Control	105	.650	.0049	.1369	.0618 + (.0160 ± .0018)	4.684	
	Post Drug	205	.575	.0037	.1345	.0758 + (.0141 ± .0014)	4.178	

(1) Significant slope difference among subjects (.025 > P > .01)

(2) Slope not significant

Regression Statistics CO_2 Output related to Minute Ventilation Derived by Covariance Analysis

Treatment Group	Period	Degree of Freedom	r	$\bar{y}$	a + b ± S.E.	$\bar{x}$	S_{yx}	Control - Post Drug Adjusted Mean ± S.E.
5 mg/70 kg (5 subjects)	Control	18	.949	.115	.0146 + (.0235 ± .0018)[1]	4.252	.0027	.0023 ± .0008 ***
	Post Drug[2]	38	.889	.108	.0175 + (.0223 ± .0018)	4.071	.0031	
10 mg/70 kg (8 subjects)	Control	31	.823	.117	.0168 + (.0211 ± .0026)[1]	4.746	.0047	-.0033 ± .0010 ***
	Post Drug[2]	62	.701	.112	.0309 + (.0187 ± .0024)[1]	4.355	.0034	
15 mg/70 kg (9 subjects)	Control	34	.848	.119	-.0088 + (.025 ± .0026)	4.645	.0027	-.0106 ± .0011 ****
	Post Drug[2]	70	.855	.102	.0107 + (.0232 ± .0017)[1]	3.943	.023	
20 mg/70 kg (4 subjects)	Control	14	.741	.121	.0081 + (.0218 ± .0051)[1]	5.186	.0033	-.0046 ± .0020 *
	Post Drug[2]	28	.703	.114	.0435 + (.0156 ± .0029)[1]	4.500	.0020	
All groups	Control	104	.860	.114	.0086 + (.0226 ± .0013)	4.684	.0035	
	Post Drug[2]	205	.814	.1083	.0202 + (.0211 ± .0010)	4.177	.0028	

(1) slopes not homogenous

(2) initial 3 post-drug observations excluded from calculation

TABLE [illegible]

[illegible] 10 15 and 20mg/70Kg [illegible] IN NORMAL SUBJECTS AND AFTER 15mg/70Kg [illegible]

WITH LEFT VENTRICULAR FAILURE

Dose	Subject	PCO_2 mm Hg Control	PCO_2 Post Drug	PCO_2 Change	PCO_2 "t" Value	PCO_2 Degrees of Freedom	pH Control	pH Post Drug	pH Change	pH "t" Value	pH Degrees of Freedom	Mean change PCO_2 [illegible]	Mean change pH [illegible]
[illegible]	[illegible]	[illegible] ([illegible])	[illegible].42+.550 ([illegible])	+.50	1.977	13	7.[illegible] ([illegible])	7.[illegible] ([illegible])	-.0355	1.705	13		
	[illegible]	[illegible] ([illegible])	[illegible] ([.323])	+3.05	5.756 ****	13	7.[illegible] ([illegible])	7.[illegible] ([illegible])	-.031	6.012 ****	13		
	[illegible]	[illegible] ([illegible])	[illegible] ([illegible])	.71	.637	13	7.[illegible] ([illegible])	7.[illegible] ([illegible])	.0103	2.701 **	13	1.30[illegible] ([illegible])	-.01[illegible] ([illegible])
	[illegible]	[illegible].107 ([illegible])	47.1[illegible] ([illegible])	+2.00	3.759 ***	13	7.41[illegible] ([illegible])	7.40[illegible] ([illegible])	-.0108	1.336	13		
	[illegible]	[illegible] ([illegible])	[illegible] ([illegible])	+1.83	.816	13	7.[illegible] ([illegible])	7.40[illegible] ([illegible])	-.0100	.571	12		
10 mg/70 Kg	[illegible]	[illegible] ([illegible])	46.6[illegible] ([illegible])	+2.65	3.0[illegible] **	8	7.[illegible] ([illegible])	7.[illegible] ([illegible])	-.0[illegible]	1.131	8		
	[illegible]	[illegible]+1.613 (1.746)	40.04+.582 ([illegible])	+3.71	2.905 **	13	7.[illegible] ([illegible])	7.[illegible] ([illegible])	-.0[illegible]	2.822	13	3.755+.509 *** (1.155)	-.029+.0093 (3) (.0180)
15 mg/70 Kg	A.M.	41.33+.[illegible] (.977)	46.67+.[illegible] (1.540)	+5.34	5.712 ****	10	7.42[illegible] ([illegible])	7.37[illegible] ([illegible])	-.0502	4.523 ***	10		
	[illegible]	41.00+.500 (.856)	44.33+.366 (1.267)	+3.33	4.247	13	7.[illegible] (.0114)	7.[illegible] ([illegible])	-.0[illegible]	.767	12		
20 mg/70 Kg	[illegible]	41.33+.716 (1.241)	44.10+.369 (1.277)	+2.77	3.375 ***	13	7.403+.0149 ([illegible])	7.369+.0[illegible] ([illegible])	-.034	2.420	13		
	J.R.	44.67+.441 (.764)	46.50+.373 (1.118)	+1.83	1.970	10	7.399+.0060 (.0085)	7.384+.0[illegible] ([illegible])	-.015	2.39[illegible] *	9	3.578+.736 (1.552)	-.0[illegible]+.0079 (.0168)
	J.D.	38.00+.289 ([illegible])	43.42+.379 (1.311)	+5.42	6.[illegible] ****	13	7.414+.0032 (.0055)	7.371+.0[illegible] ([illegible])	-.043	2.370 *	13		
	[illegible]	41.67+.[illegible] ([illegible])	45.96+.454 (1.573)	+4.29	4.578 ****	12	7.406+.0006 (.0010)	7.354+.0065 (.0224)	-.052	3.[illegible] ***	13		
Left Ventricular Failure 15mg/70 Kg	[illegible]	43.[illegible] ([illegible])	49.33+.648 (2.148)	+6.17	4.[illegible] ****	12	7.416+.0050 (.0087)	7.363+.0035 (.0117)	-.045	[illegible] ****	13		
	[illegible]	33.00+.289 ([illegible])	45.83+.782 ([illegible])	+12.83	9.125 ****	10	7.483+.0067 (.0117)	7.413+.0072 (.0217)	-.070	5.209 ****	18		
	[illegible]	[illegible]	[illegible]	+[illegible]	21.7[illegible] **	10	[illegible]	[illegible]	-.108	4.555 **	[illegible]		

(1) [illegible] and 15mg/70Kg groups treated as one combined group;

(2) [illegible] change not significant at (P - .[illegible]) [illegible];

(3) [illegible] in pH just short of significance at .05 level

Table 18

Alveolar ventilation, dead space ventilation, dead space volume (physiological) and $PaCO_2$ at successive 4 minute intervals - normal subjects and subjects in left ventricular failure

Dose of Drug	Subject	Item	CONTROL PERIODS			POST DRUG PERIODS											
			1	2	3	1	2	3	4	5	6	7	8	9	10	11	12
Normal subjects 5 mg/70 kg	F.G.	$\dot{V}_A$	2.877	2.910	2.747	2.851	2.862	2.790	3.024	2.782	2.676	2.850	2.828	2.903	2.703	2.601	**2.864**
		$\dot{V}_D$	0.969	1.079	1.211	0.914	0.952	0.960	1.077	1.090	1.132	1.044	1.101	1.198	1.427	1.451	**1.373**
		V_D	0.0825	0.0814	0.0881	0.0665	0.0630	0.0711	0.0706	0.0727	0.0742	0.0696	0.0722	**0.0737**	0.0804	0.0866	**0.0820**
		$PaCO_2$	43	43	46	41	42	43	42	43	44	42	43	42	455	46.5	**45.5**
	M.W.	$\dot{V}_A$	2.748	3.680	2.569	5.572	2.960	2.879	2.371	**2.604**	2.398	2.805	**2.470**	2.814	2.670	2.556	**2.875**
		$\dot{V}_D$	1.280	1.397	1.305	2.437	1.654	1.366	1.348	1.440	1.152	1.485	1.075	1.610	1.369	1.190	**1.432**
		V_D	0.0883	0.0822	0.0900	0.1189	0.0894	0.0867	0.0856	0.0944	0.0922	0.0928	0.0811	0.0961	0.0883	0.0850	**0.0889**
		$PaCO_2$	41	37.5	41.0	32.5	39	39.5	43.5	44	42.5	42	42.5	44.5	42	42.5	**43**
	G.R.	$\dot{V}_A$	2.842	2.915	2.808	2.915	2.639	2.395	2.573	2.351	2.513	2.786	3.007	2.873	2.714	2.790	**2.816**
		$\dot{V}_D$	1.331	1.321	1.411	1.444	1.488	1.300	1.245	1.198	1.259	1.290	1.424	1.322	1.235	1.200	**1.219**
		V_D	0.0819	0.0813	0.0868	0.0902	0.0945	0.0912	0.0871	0.0811	0.0868	0.0890	0.0934	0.0912	0.0852	0.0857	**0.0813**
		$PaCO_2$	45	45	45.5	45.5	48.5	47.5	46.5	47	48.5	47.5	47.5	47	47.5	47	**46**
	W.B.	$\dot{V}_A$	3.597	3.632	3.373	4.384	3.218	2.680	3.241	2.941	3.164	3.915	3.105	3.309	3.184	2.864	**2.928**
		$\dot{V}_D$	1.152	1.151	1.157	0.926	1.030	1.049	**1.121**	1.217	1.330	1.296	1.180	1.287	0.869	1.075	**0.926**
		V_D	0.0768	0.0921	0.0890	0.0805	0.0841	0.0823	**0.0787**	0.0854	0.0902	0.0823	0.0774	0.0780	0.0695	0.0860	**0.0726**
		$PaCO_2$	38.25	37.5	37.5	34.2	38.5	40.75	40	41	39.5	36	39	38.5	37.75	36	**38.5**
	W.S.	$\dot{V}_A$	2.972	2.986	3.862	2.714	2.605	2.631	2.600	2.525	2.584	2.545	2.495	2.427	2.480	2.460	**2.480**
		$\dot{V}_D$	1.549	1.558	1.533	1.491	1.525	1.438	1.492	1.491	1.508	1.609	1.600	1.405	1.533	1.515	**1.549**
		V_D	0.1016	0.0989	0.1022	0.0962	0.1000	0.0913	0.0995	0.0978	0.0989	0.1038	0.1049	0.0892	0.0989	0.0962	**0.0968**
		$PaCO_2$	44	43.5	44	45	46.5	45.5	47	47	47	47	48	47	47.3	47	**48**
10 mg/70 kg	G.F.	$\dot{V}_A$	3.346	3.725	3.746	3.774	3.084	3.262	3.072	3.235	2.882	3.174					
		$\dot{V}_D$	1.624	1.850	1.845	2.120	1.615	1.571	1.484	1.735	1.719	1.889					
		V_D	0.0802	0.0881	0.0802	0.0757	0.0751	0.0757	0.0836	0.0938	0.0955	0.0994					
		$PaCO_2$	43.75	43.75	44.28	44.25	45.75	45.75	46.5	47.25	48.25	48.25					
	A.McK.	$\dot{V}_A$	2.879	3.515	3.711	3.297	2.998	3.028	3.149	3.330	3.188	3.445	3.377	3.169	3.941	2.915	**2.836**
		$\dot{V}_D$	2.922	2.322	2.226	2.210	1.848	1.944	2.114	2.026	1.974	1.778	2.239	2.161	2.139	2.315	**2.308**
		V_D	0.1067	0.1290	0.1187	0.1228	0.1192	0.1275	0.1321	0.1228	0.1316	0.1166	0.1337	0.1394	0.1337	0.1518	**0.1539**
		$PaCO_2$	34.5	36.0	36.5	37.5	38	41.5	40	38	40	38.5	39.5	39.5	41	43.5	**43.5**
15 mg/70 kg	H.S.	$\dot{V}_A$	3.048	3.125	3.050	2.210	2.226	2.392	2.578	2.721	2.600	2.400	2.863	2.935	2.751	2.651	**2.828**
		$\dot{V}_D$	1.947	1.884	1.859	1.343	1.185	1.176	1.389	1.374	1.495	1.396	1.382	1.246	1.130	1.173	**1.367**
		V_D	0.1025	0.0954	0.1005	0.0853	0.0878	0.0797	0.0868	0.0964	0.0949	0.0980	0.0888	0.0817	**0.0807**	0.0838	**0.0959**
		$PaCO_2$	42	40.5	40.5	44.5	45.5	44.5	44.5	44.5	45	47	44.5	42.5	42.5	43	**44**
	A.D.	$\dot{V}_A$	3.130	2.924	2.913	2.561	2.454	2.557	2.554	2.600	2.623	2.506	2.562	2.593			
		$\dot{V}_D$	1.619	1.368	1.399	1.421	1.195	1.195	1.239	1.290	1.267	1.343	1.370	1.359			
		V_D	0.0762	0.0720	0.0746	0.0693	0.0646	0.0646	0.0698	0.0688	0.0667	0.0746	0.0794	0.0788			
		$PaCO_2$	41	41	42	43.5	46.0	45.5	47.0	47.0	46.5	48	48	48.5			
20 mg/70 kg	W.F.	$\dot{V}_A$	3.733	3.473	3.642	3.019	2.927	3.111	3.060	2.978	2.983	2.981	3.095	3.213	3.016	3.022	**2.984**
		$\dot{V}_D$	1.997	2.195	1.820	1.716	1.420	1.546	1.505	1.581	1.634	1.867	1.799	1.696	1.902	1.835	**1.857**
		V_D	0.0878	0.0944	0.0800	0.0817	0.0778	0.0788	0.0783	0.0772	0.0811	0.0817	0.0889	0.0867	0.0789	0.0928	**0.0906**
		$PaCO_2$	42	42	40	42.5	43.5	42.5	42.5	45.5	45	45.25	45	45.25	45	45	**45**
	C.R.	$\dot{V}_A$	3.277	3.100	3.079	2.509	2.639	2.888	2.864	2.762	2.773	2.913	2.957	2.924	2.734	2.710	**2.698**
		$\dot{V}_D$	1.732	1.784	1.706	1.503	1.567	1.333	1.370	1.500	1.399	1.357	1.425	1.486	1.603	1.542	**1.666**
		V_D	0.0949	0.1005	0.0975	0.0859	0.0995	0.0874	0.0843	0.0909	0.0823	0.0798	0.0838	0.0874	0.0929	0.0949	**0.1010**
		$PaCO_2$	42	41.5	41.5	43.5	46	45	45	46	45	45.5	45	45.5	48.5	48.5	**48**
	A.D.	$\dot{V}_A$	3.427	3.208	3.476	2.825	2.849	3.068	3.021	3.079	2.948	2.849	2.940	3.045	2.998	3.056	**2.816**

		$\dot{V}_A$															
		$\dot{V}_D$															
		V_D															
		$PaCO_2$															
15 mg/70 kg	H.J.	$\dot{V}_A$	3.048	3.125	3.050	2.210	2.226	2.392	2.578	2.721	2.600	2.400	2.853	2.935	2.761	2.851	2.828
		$\dot{V}_D$	1.947	1.884	1.859	1.343	1.185	1.170	1.389	1.371	1.495	1.390	1.382	1.240	1.130	1.173	1.367
		V_D	0.1025	0.0951	0.1005	0.0853	0.0878	0.0797	0.0868	0.0951	0.0949	0.0980	0.0888	0.0817	0.0807	0.0838	0.0959
		$PaCO_2$	38	39.5	40.5	44.5	45.5	44.5	44.5	44.5	45	47	44.5	42.5	42.5	43	44
	[illegible]	$\dot{V}_A$	[illegible]	3.041	3.010	2.561	2.154	2.557	2.551	2.300	2.323	2.506	2.562	2.593			
		$\dot{V}_D$	[illegible]	1.369	1.399	1.421	1.195	1.195	1.239	1.199	1.267	1.243	1.370	1.369			
		V_D	0.0752	0.0720	0.0740	0.0693	0.0646	0.0646	0.0693	0.0638	0.0667	0.0746	0.0794	0.0788			
		$PaCO_2$	41	41	42	43.5	45.0	45.5	47.0	47.0	46.5	48	48	48.5			
30 mg/70 kg	W.F.	$\dot{V}_A$	3.733	3.473	3.643	3.019	2.927	3.111	3.060	2.978	2.983	2.981	3.095	3.213	3.016	3.022	2.984
		$\dot{V}_D$	1.927	2.195	1.830	1.716	1.420	1.545	1.505	1.581	1.634	1.837	1.799	1.696	1.902	1.835	1.857
		V_D	[illegible]	0.0941	0.0884	0.0817	0.0778	0.0788	0.0783	0.0772	0.0811	0.0817	0.0889	0.0867	0.0789	0.0928	0.0906
		$PaCO_2$	[illegible]	40	40	42.5	43.5	43.5	42.5	45.5	45	45.25	45	45.25	45	45	45
	[illegible]	$\dot{V}_A$	[illegible]	3.178	3.078	2.839	2.639	2.883	2.834	2.702	2.773	2.913	2.957	2.924	2.734	2.710	2.698
		$\dot{V}_D$	1.702	1.734	1.781	[illegible]	1.567	1.333	1.376	1.500	1.399	1.357	1.425	1.486	1.603	1.542	1.666
		V_D	0.0949	0.1005	0.0934	0.0859	0.0895	0.0874	0.0843	0.0909	0.0823	0.0798	0.0838	0.0874	0.0929	0.0949	0.1010
		$PaCO_2$	42	41.5	41.5	42.5	43	43	45	43	45	45.5	45	45.5	48.5	48.5	48
	J.D.	$\dot{V}_A$	3.127	3.327	3.476	2.825	2.849	3.068	3.021	3.079	2.948	2.843	2.940	3.045	2.998	3.056	2.816
		$\dot{V}_D$	2.030	3.130	2.219	2.056	1.931	1.979	2.073	2.031	1.940	1.929	2.020	2.168	2.215	2.094	2.191
		V_D	[illegible]	0.1041	0.1155	0.1348	0.1348	0.1365	0.1382	0.1351	0.1315	0.1354	0.1393	0.1399	0.1477	0.1444	0.1511
		$PaCO_2$	37.5	38.5	43	40.5	42.5	42.5	43	43	43	44	44	44	45.5	44	45
	J.R.	$\dot{V}_A$	3.003	2.837	3.306	2.564	2.162	2.381	2.390	2.456		2.601		2.623			
		$\dot{V}_D$	1.792	1.750	1.768	1186	1.073	1.007	1.148	1.150		1.206		1.215			
		V_D	0.1156	0.1094	0.1156	0.0833	0.0894	0.0839	0.0883	0.0939		0.0928		0.0917			
		$PaCO_2$	46.5	44.5	44	44	47.5	47	47,5	47	47	46.5	46.5	45.5			
Left Ventricular Failure 15 mg/70 kg	L.G.	$\dot{V}_A$	4.707	4.690	4.235	3.705	2.430	2.272	2.616	2.411	2.379	2.504	2.314	2.598			
		$\dot{V}_D$	3.356	3.306	1.918	2.514	1.185	0.893	1.345	1.468	1.349	1.469	1.443	1.375			
		V_D	0.1160	0.1126	0.1045	0.1257	0.0677	0.0533	0.0737	0.0725	0.0683	0.0653	0.0671	0.0611			
		$PaCO_2$	30.5	31.0	31	28.5	35.5	38.5	44	47	47	50	50	49.5			
	A.M.	$\dot{V}_A$	2.905	3.600	3.910	3.287	2.956	2.612	2.943	2.892	2.708	2.426	2.652	2.419	2.559	3.095	
		$\dot{V}_D$	4.560	3.458	3.076	3.295	3.151	3.662	2.760	2.976	2.592	2.683	2.528	2.737	2.906	3.487	
		V_D	0.1689	0.1305	0.1183	0.1146	0.1146	0.1238	0.1299	0.1280	0.1280	0.1293	0.1280	0.1335	0.1384	0.1500	
		$PaCO_2$	44.5	42.5	42.5	[illegible]	48	49.5	49	46.5	49.5	50.5	49	54	50	50.5	
		$\dot{V}_A$	[illegible]	[illegible]	3.691	2.422	1.749	2.314	2.307	2.134	2.293	2.385	2.408				
		$\dot{V}_D$	1.220	4.303	4.556	3.157	2.444	2.952	3513	2.919	3.251	2.808	2.628				
		V_D	[illegible]	0.1314	0.1402	0.1226	0.1377	0.1440	0.1849	0.1497	0.1667	0.1478	0.1440				
		$PaCO_2$	[illegible]	33	33.5	45.5	48.5	46.5	47	48	45.5	43.5	41				

Table 19

Regression Statistics $PaCO_2$ / Alveolar ventilation - Normal Subjects

Treatment Group	Period	r	Degrees of Freedom	S_{yx}	$\bar{Y}$	a + (b ± S.E.)	$\bar{X}$	Control - Post drug adjusted mean ± S.E.	t values for b	P
Common Control[1]		-.507	21	.8731	41.689	47.809 - (1.938 ± .719)**	3.157		2.695	.02 > P > .01
5 mg/70 kg	Post Drug	-.397	50	1.2810	43.786	50.044 - (2.259 ± .739)***	2.770	-.899 ± .368**	3.057	.01 > P > .001
10 mg/70 kg	Post Drug	-.362	15	1.7234	42.347	50.433 - (2.537 ± 1.685)	3.188	-1.950 ± 1.049[2]	1.506	.2 > P > .1
15 mg/70 kg	Post Drug	-.400	18	1.3081	45.333	52.961 - (2.958 ± 1.599)	2.579	-3.106 ± .399****	1.850	.1 > P > .05
20 mg/70 kg	Post Drug	-.236	38	1.3539	44.808	52.700 - (2.772 ± 1.852)	2.847	-.2.288 ± .417****	1.497	.2 > P > .1
Common Post-drug regression		-.350	124	1.3544	44.152	51.074 - (2.456 ± .591)****	2.819		4.156	P < .001

(1) 10 mg/70 kg group excluded because of significant slope difference

(2) Post Drug adjusted mean compared with 10 mg/70 kg control estimate

Table 20

Regression Statistics Alveolar ventilation/$PaCO_2$ Normal subjects

Treatment Group	Degrees of Freedom	S_{yx}	$\bar{Y}$	$a + (b \pm S.E.)$	$\bar{x}$	Remarks
Pooled Control	21	.2283	3.157	8.6807 - (.1325 ± .0492)**	41.689	
5 mg/70 kg Post drug	50	.2250	2.770	5.8219 - (.0697 ± .0238)***	43.786	Post drug slope not significantly different from control. Post drug adjusted mean significantly less than control (.2157 ± .0618).
10 mg/70 kg post drug	15	.2548	3.188	5.3773 - (.0517 ± .0356)	42.347	Post drug slope is significantly smaller than own control slope.
15 mg/70 kg post drug	18	.1768	2.579	5.0270 - (.0540 ± .0292)	45.333	Post drug slope not significantly different from control. Post drug adjusted mean significantly less than control (.1653 ± .0941).
20 mg/70 kg post drug	38	.1152	2.847	3.7476 - (.0201 ± .0187)	44.808	Post drug slope significantly different from control slope (.05 > P > .02).
Common regression	124	.1928	2.819	5.0178 - (.0498 ± .0120)****	44.152	

TABLE XI

MINUTE VENTILATION, RESPIRATORY RATE, TIDAL VOLUMES, O_2 UPTAKE AND CO_2 EXCRETION (~~EXPIRED AIR~~)

MEASUREMENTS DURING SUCCESSIVE FOUR MINUTE PERIODS BEFORE AND AFTER MORPHINE 15mg/70Kg

IN PATIENTS WITH LEFT VENTRICULAR FAILURE

Age / Sex / Subject / S.A. / Ht. / Wt.	Measurement	Control Periods			Mean Control	Post Drug Periods											
		1	2	3	Values	1	2	3	4	5	6	7	8	9	10	11	12
61 yrs M A.O. 1.82sq.m. 173cms. 70Kg	Minute Ventilation	4.533	4.481	4.220	4.413	4.882	3.881	3.896	3.511	3.896	3.557	3.557	4.158	3.850	4.081	3.434	3.821
	Respiratory Rate	19.25	16.25	16.25	17.25	17.50	13.75	12.25	11.25	11.75	9.33	10.25	12.25	10.25	11.25	10.25	9.50
	Tidal Volumes	.436	.495	.494	.4752	.496	.492	.596	.575	.580	.630	.611	.609	.658	.658	.580	.662
	O_2 Uptake	.130	.136	.127	.1310	.140	.125	.128	.116	.132	.116	.126	.131	.128	.135	.114	.136
	CO_2 Excretion	.162	.167	.162	.1637	.189	.155	.161	.147	.168	.158	.157	.180	.163	.182	.149	.169
30 yrs. M D.McA. 1.77sq.m. 168cms. 68.5Kg	Minute Ventilation	8.660	8.726	8.550	8.646	7.969	7.133	7.397	7.529	7.198	6.449	6.560	6.164	6.296	6.207	6.383	6.097
	Respiratory Rate	27.50	26.25	26.00	26.58	26.25	26.50	23.50	23.25	24.00	22.75	19.75	20.75	22.75	19.50	22.50	22.75
	Tidal Volumes	.557	.577	.571	.568	.514	.472	.558	.565	.546	.490	.579	.511	.487	.506	.480	.452
	O_2 Uptake	.176	.184	.177	.1790	.185	.168	.182	.185	.172	.167	.182	.169	.164	.158	.154	.148
	CO_2 Excretion	.283	.285	.279	.2823	.276	.245	.266	.279	.258	.233	.265	.241	.243	.240	.244	.227
60yrs. M R. McI. 1.73sq.m. 169cms. 65Kg	Minute Ventilation=	4.561	4.432	4.465	4.485	3.707	3.284	3.639	2.737	3.329	3.217	3.667	2.911	3.426	4.052	5.210	3.763
	Respiratory Rate	16.00	15.75	16.50	16.08	16.25	14.25	13.25	12.75	12.75	13.50	14.50	14.00	14.50	13.50	12.75	14.50
	Tidal Volumes	.480	.441	.458	.4592	.382	.387	.462	.345	.440	.414	.430	.343	.407	.479	.673	.421
	O_2 Uptake	.125	.116	.126	.1223	.098	.113	.120	.090	.110	.101	.113	.082	.115	.128	.127	.103
	CO_2 Excretion	.178	.166	.171	.1717	.137	.138	.158	.114	.145	.136	.157	.113	.147	.179	.204	.143
62 yrs. M A.M. 1.64sq.m. 165sq.m. 59Kg	Minute Ventilation	7.365	7.058	6.986	7.137	6.582	6.107	5.274	5.703	5.868	5.300	5.109	5.180	5.156	5.465	6.582	6.915
	Respiratory Rate	27.00	26.50	26.00	26.50	28.75	27.50	21.50	21.25	23.25	20.25	20.75	19.75	20.50	21.00	23.25	26.50
	Tidal Volumes	.533	.441	.412	.4619	.372	.371	.408	.427	.424	.424	.407	.421	.414	.434	.474	.434
	O_2 Uptake	.149	.142	.147	.1460	.136	.140	.132	.135	.131	.127	.115	.123	.123	.116	.142	.137
	CO_2 Excretion	.215	.203	.204	.2073	.180	.173	.166	.180	.177	.170	.152	.163	.162	.165	.211	.198
71 yrs. F E.S. 1.59sq.m. 165cms. 55Kg	Minute Ventilation	7.860	8.100	8.247	7.968	5.579	4.193	5.264	5.720	5.053	5.544	5.193	5.036	5.019	5.176	4.497	5.193
	Respiratory Rate	34.50	32.75	32.50	33.25	25.75	17.75	20.50	19.00	19.50	19.50	19.00	18.25	19.00	18.75	14.25	18.75
	Tidal Volumes	.371	.392	.409	.3905	.336	.379	.407	.491	.407	.454	.426	.433	.411	.457	.473	.441
	O_2 Uptake	.104	.110	.113	.1090	.094	.092	.107	.106	.094	.104	.096	.098	.089	.100	.086	.104
	CO_2 Excretion	.137	.145	.147	.1430	.106	.100	.122	.130	.112	.123	.120	.119	.112	.122	.106	.126
60 yrs. F A.G. 1.67sq.m. 154cms. 68.7Kg	Minute Ventilation	7.123	7.056	6.148	6.776	8.246	3.615	3.165	3.961	3.879	3.728	3.973	3.757	3.973	3.890	3.807	4.305
	Respiratory Rate	20.75	20.00	18.25	19.67	20.00	17.50	16.75	18.25	20.25	19.75	22.50	21.50	22.50	21.00	22.50	21.75
	Tidal Volumes	.602	.597	.576	.5918	.672	.345	.330	.356	.332	.322	.301	.310	.294	.312	.308	.353
	O_2 Uptake	.156	.161	.158	.1583	.153	.115	.140	.163	.159	.153	.149	.147	.147	.146	.141	.137
	CO_2 Excretion	.229	.224	.204	.2190	.244	.116	.121	.154	.151	.146	.158	.152	.160	.157	.154	.168

Table 22

Control values in Normal Subjects and Patients with Left Ventricular Failure

Measurement	NORMAL SUBJECTS				Patients in Left Ventricular Failure		Difference between means	
	All Normals		Normals in 15 mg/70 kg Treatment group					
	n	Mean ± S.E. (S.D.) (1)	n	Mean ± S.E. (S.D.) (2)	n	Mean ± S.E. (S.D.) (3)	(3) - (1)	(3) - (2)
Ventilation	28	4.674 ± .1095 (.5796)	9	4.677 ± .1573 (.4717)	6	6.571 ± .7217 (1.7681)	1.897**	1.894*
Respiratory Rate	28	16.52 ± .57 (3.01)	9	17.28 ± 1.01 (3.02)	6	23.22 ± .85 (2.09)	670****	5.94***
Tidal Volume	28	.5252 ± .0157 (.0832)	9	.4938 ± .0300 (.0901)	6	.4911 ± .0307 (.0752)	-.0341	-.0027
Oxygen Uptake	26	.1376 ± .0030 (.0154)	9	.1312 ± .0048 (.0145)	6	.1409 ± .0104 (.0255)	.0033	.0097
Carbon dioxide output	26	.2724 ± .0053 (.0270)	9	.2023 ± .0112 (.0037)	6	.1978 ± .0204 (.0501)	-.0146	-.0045
Age	28	45.32 ± 2.20 (11.64)	9	53.66 ± 3.32 (9.95)	6	57.33 ± 5.72 (14.02)	12.01*	3.67
Control Variability								
Minute Ventilation	28	.0738 ± .0076 (.0404)	9	.0585 ± .0089 (.0268)	6	.0927 ± .0178 (.0436)	.0189	.0342
Oxygen Uptake	26	.0275 ± .0033 (.0170)	9	.0276 ± .0055 (.0157)	6	.0312 ± .0046 (.0114)	.0037	.0036

n = number of subjects

Table 23

Changes in PaO_2, $PaCO_2$ and arterial pH after 15 mg/70 kg morphine in patients with left ventricular failure

Subject	Changes in PaO_2		Changes in $PaCO_2$		Changes in arterial pH	
	Control	Post drug	Control	Post drug	Control	Post drug
A.M.	69.33 ± 1.45 (2.52)	69.18 ± 2.74 (9.09)	43.17 ± .67 (1.16)	49.32 ± .65**** (2.15)	7.416 ± .005 (.009)	7.36 ± .003**** (.012)
E.S.	96.67 ± 1.33 (2.31)	58.67 ± 2.01**** (6.04)	33.00 ± .30 (.50)	45.83 ± .78**** (2.34)	7.483 ± .0067 (.012)	7.413 ± .007**** (.022)
A.G.	82.33 ± 1.45 (2.52)	64.33 ± 4.30** (12.90)	30.83 ± .17 (.29)	43.33 ± 2.52** (7.57)	7.532 ± .006 (.010)	7.424 ± .020** (.060)

TABLE 24

CHANGES IN MINUTE VENTILATION, RESPIRATORY RATE, TIDAL VOLUME, O_2 UPTAKE AND CO_2 EXCRETION IN PATIENTS WITH LEFT VENTRICULAR FAILURE AFTER 15mg/70Kg MORPHINE

NAME	Minute Ventilation					Respiratory Rate					Tidal Volume					O_2 Uptake					CO_2 Excretion				
	CONTROL	POST DRUG	CHANGE	't' VALUE	DEGREES OF FREEDOM	CONTROL	POST DRUG	CHANGE	't' VALUE	DEGREES OF FREEDOM	CONTROL	POST DRUG	CHANGE	't' VALUE	DEGREES OF FREEDOM	CONTROL	POST DRUG	CHANGE	't'VALUE	DEGREES OF FREEDOM	CONTROL	POST DRUG	CHANGE	't' VALUE	DEGREES OF FREEDOM
A.G.	4.413±.1949 (.6751)	3.879±.1368 (.9475)	.534	1.834	58	17.25±.697 (2.417)	11.68±.461 3.162)	-5.57	5.678***	57	.4752±.0207 (.0717)	.5955±.0159 (.1100)	+.1203	3.591***	58	.1310±.0026 (.0046)	.1271±.0031 (.0108)	-.0039	1.604	13	.1637±.0017 (.0029)	.1648±.0038 (.0132)	+.0011	.139	
D.McA.	8.646±.0664 (.2301)	6.782±.1154 (.7996	1.864	7.945***	58	26.58±.260 (.900)	23.00±.357 (2.422)	-3.58	5.000***	56	.5680±.0036 (.0124)	.5131±.0087 (.0606)	-.0549	3.102***	58	.1790±.0025 (.0040)	.1695±.0036 (.0123)	-.0095	1.284	13	.2823±.0018 (.0031)	.2514±.0049 (.0169)	-.0309	3.069***	
R.M.	4.485±.1291 (.4473)	3.579±.1114 (.7717)	-.906	5.850***	58	15.08±.313 (1.084)	13.88±.199 (1.377)	-2.20	5.135***	58	.4892±.0177 (.0613)	.4319±.0155 (.1073)	-.0273	1.162	30	.1223±.0032 (.0055)	.1083±.0041 (.0141)	-.0140	1.652	13	.1717±.0035 (.0060)	.1467±.0073 (.0253)	-.0241	1.596	
A.M.	7.137±.2442 (.8459)	5.770±.1530 (1.0602)	-1.367	4.139***	58	26.50±.358 (1.243)	22.85±.544 (3.770)	-3.65	3.291***	58	.4619±.0259 (.0897)	.4173±.0076 (.0528)	-.0446	1.652	13	.1460±.0021 (.0036)	.1298±.0026 (.0090)	-.0162	2.996***	13	.2073±.0039 (.0067)	.1748±.0047 (.0163)	-.0325	3.316***	
E.S.	7.968±.1494 (.5176)	5.175±.1545 (1.0592)	-2.793	8.825***	58	33.25±.446 (1.544)	19.17±.506 (3.503)	-14.08	13.525***	58	.3908±.0084 (.0327)	.4262±.0095 (.0660σ	+.0357	2.660**	36	.1090±.0026 (.0046)	.0975±.0020 (.0068)	-.0115	2.738***	13	.1430±.0031 (.0053)	.1165±.0026 (.0092)	-.0265	4.724***	
A.G.	6.775±.1831 (.6341)	4.191±.2519 (1.7453)	-2.585	5.019***	58	19.67±.497 (1.727)	20.35±.425 (2.942)	+0.68	.765	58	.5018±.0209 (.0724)	.3529±.0174 (.1208)	-.2389	6.533***	58	.1583±.0015 (.0025)	.1458±.0036 (.0123)	-.0125	1.712	13	.2190±.0076 (.0132)	.1568±.0091 (.0314)	-.0622	3.281***	

TABLE 24a

CHANGES IN MINUTE VENTILATION, RESPIRATORY RATE, TIDAL VOLUME, O_2 UPTAKE AND CO_2 EXCRETION

AFTER 15mg/70Kg IN PATIENTS WITH LEFT VENTRICULAR FAILURE

DOSE	SUBJECT	Minute Ventilation		Respiratory Rate		Tidal Volume		O_2 Uptake		CO_2 Excretion	
		ACTUAL CHANGE	FRACTIONAL CHANGE	ACTUAL CHANGE	FRACTIONAL CHANGE	ACTUAL CHANGE	FRACTIONAL CHANGE	ACTUAL CHANGE	FRACTIONAL CHANGE	ACTUAL CHANGE	FRACTIONAL CHANGE
		L/sq.m.		Breath/min.		L. B.T.P.S.		l/min./sq.m. S.T.P.D.		l/min. S.T.P.D.	
15mg/70Kg L.V.F.	A.O.	-0.534	-.1210	-5.57	-.3229	+.120	+.2532	-.0039	-.0298	+.0011	+.0067
	D.MCA.	-1.864	-.2156	-3.58	-.1347	-.055	-.0968	-.0095	-.0531	-.0309	-.1095
	R.McI.	-0.906	-.2020	-2.20	-.1368	-.027	-.0595	-.0140	-.1145	-.0241	-.1404
	A.M.	-1.367	-.1915	-3.65	-.4235	-.045	-.0966	-.0162	-.1110	-.0325	-.1568
	E.S.	-2.793	-.3505	-14.08	-.1377	+.036	+.0914	-.0115	-.1055	-.0265	-.1853
	A.G.	-2.585	-.3815	+0.68	+.0346	-.239	-.4037	-.0125	-.0790	-.0622	-.2840

Table 25

Fractional Depression in Respiration, Oxygen Uptake and Carbon Dioxide Output, in Patients with Left Ventricular Failure (6 subjects) Compared with normal subjects given 15 mg/70 kg (9 subjects)

Measurement	Fractional Changes		P value for difference (2) - (1)
	Normals (1)	Left Ventricular Failure (2)	
Minute Ventilation	.1611 ± .0195**** (.0584)	.2437 ± .0411*** (.1007)	.1 > P > .05 (.05 nearly)
Respiratory Rate	.1281 ± .0287*** (.0862)	.868 ± .0661* (.1619)	P > .3
Tidal Volume	.0151 ± .0212 (.0635)	.0520 ± .0897 (.2197)	P = .7
Oxygen Uptake	.0230 ± .0152 (.0455)	.0822 ± .0142*** (.0347)	.02 > P > .01
Carbon Dioxide Output	.0803 ± .0157**** (.0472)	.1449 ± .0389** (.0953)	P = .1

Table 26

Regression Statistics Oxygen Uptake/Ventilation in Patients with Left Ventricular Failure

Treatment Group	r	Degrees of Freedom	S_{yx}	$\bar{Y}$	a + (b ± S.E.)	$\bar{X}$	Difference between adjusted means	
							Groups tested	Difference ± S.E.
1. Control Regression(1)	.620	19	.0039	.1362	.0550 + (.0124*** ± .0036)	6.568	1 - 2	-.0212 ± .0024****
2. Post Drug Regression	.715	47	.0074	.1291	.0553 + (.0154 ± .0022)	4.779	1 - 3	-.0368 ± .0024****
3. Control - all normals	.650	105	.0049	.1369	.0618 + (.0160 ± .0018)	4.684		

(1) One subject (A.G.) exhibited because of significant slope difference.

Table 27

Control Observations
(Normal Subjects)

Comparisons between Soluble Phenobarbitone and Morphine Treatment Groups

Measurement	Morphine Group		Soluble Phenobarbitone Group		Difference (1 - 2)	P value
	n	Mean ± S.E. (S.D.)	n	Mean ± S.E. (S.D.)		
Ventilation	28	4.674 ± .1095 (.5796)	4	4.482 ± .3759 (.7519)	.1923	7.5
Respiratory Rate	28	16.52 ± .5689 (3.0102)	4	17.96 ± 1.60 (3.19)	-1.44	.4 > P > .3
Tidal Volume	28	.5252 ± .0157 (.0832)	4	.4529 ± .0400 (.0800)	.0723	.2 > P > .1
Oxygen Uptake	26	.1376 ± .0030 (.0154)	4	.1190 ± .0019 (.0038)	.0186*	.05 > P > .02
Carbon dioxide output	26	.2124 ± .0053 (.0270)	4	.1834 ± .0067 (.0133)	.0290*	.05 > P > .02
Age	28	45.32 ± 2.20 (11.64)	4	51 ± 5.92 (11.83)	-5.68	.4 > P > .3

n = number of observations

CHANGES IN MINUTE VENTILATION, RESPIRATORY RATE, TIDAL VOLUME, O_2 UPTAKE, CO_2 EXCRETION IN NORMALS AFTER SOLUBLE PHENOBARBITONE

NAME DOSE	Minute Ventilation					Respiratory Rate					Tidal Volume					O_2 Uptake					CO_2 Excretion				
	CONTROL	POST DRUG	CHANGE	't' VALUE	DEGREES OF FREEDOM	CONTROL	POST DRUG	CHANGE	't' VALUE	DEGREES OF FREEDOM	CONTROL	POST DRUG	CHANGE	't' VALUE	DEGREES OF FREEDOM	CONTROL	POST DRUG	CHANGE	"t"value	DEGREES OF FREEDOM	CONTROL	POST DRUG	CHANGE	"T"VALU	
G.M. 3.5mg/Kg	4.408±.0550 (.1627)	4.469±.0495 (.3732)	+.061	.628	58	21.25±.592 (2.05)	20.11±.290 (1.335)	-1.14	2.321	555	.3379±.0075 (.0259)	.3693±.0045 (.0316)	+.0314	3.***161	58	.1213±.0013 (.0023)	.1219±.0009 (.0031)	+.0006	.306	DEGREES 18	.1720±.0021 (.0036)	.1801±.0021 (.0073)	CHAN .0081	1.831	
A.M. 3.6mg/Kg	5.355±.1710 (.5922)	5.514±.0713 (.1939)	+.158	.954	58	18.50±.289 (1.00)	18.43±.131 (.903)	-.07	.235	57	.5042±.0166 (.0574)	.5247±.0074 (.0511)	+.0205	1.213	58	.1170±.0040 (0070)	.1173±.0015 (.0054)	+.0003	.082	13	.1797±.0068 (.0018)	.1803±.0026 (.0097)	+.0046	.708	
A.M. 3.1mg/Kg	3.531±.0774 3.(.2681)	3.429±.0413 (.2864)	-.101	1.106	58	13.58±.193 (.669)	13.35±.117 (.812)	-.23	.902	58	.5103±.0010 (.0380)	.5035±.0062 (.0129)	-.0068	.500	58	.1147±.0009 (.0016)	.1131±.0010 (.0033)	-.0016	.800	13	.1793±.0019 (.0032)	.1763±.0015 (.0051)	-.003	.252	
J.C. 3.1mg/Kg	4.633±.0413 (.1429)	4.173±.0401 (.2780)	+.160	****5.523	58	18.50±.230 (.798)	16.34±.183 (1.255)	-2.16	****5.651	57	.4592±.0045 (.0158)	.4654±.0038 (.0363)	+.0062	.779	58	.1230±.0006 (.0010)	.1128±.0014 (.0047)	-.0102	***3.630	13	.2027±.0012 (.0021)	.1854±.0026 (.0091)	-.0173	***3.204	

TABLE 28A

MINUTE VENTILATION, RESPIRATORY RATE, TIDAL VOLUMES, O_2 UPTAKE, CO_2 EXCRETION (~~EXPIRED AIR~~)

MEASUREMENTS DURING SUCCESSIVE FOUR MINUTE PERIODS BEFORE AND AFTER SOLUBLE PHENOBARBITONE

(3.1 - 3. mg/Kg)

Age / Name / S.A. / Ht.	Sex / Wt.	Measurement	Control Periods 1	2	3	Mean Control Value	Post Drug Periods 1	2	3	4	5	6	7	8	9	10	11	12
38 yrs.	M	Minute Ventilation	4.435	4.339	4.452	4.408	4.414	4.435	4.291	4.653	4.403	4.516	4.195	4.388	4.371	4.467	4.724	4.580
		Respiratory Rate	21.75	20.25	21.75	21.25	20.00	19.75	21.50	18.75	19.25	20.00	20.25	21.25	20.50	20.50	20.25	19.25
G.M.		Tidal Volumes	.336	.353	.324	.3379	.346	.358	.334	.414	.377	.398	.356	.354	.361	.367	.387	.380
1.74sq.m.		O_2 Uptake	.120	.124	.120	.1213	.124	.118	.118	.129	.122	.122	.121	.120	.121	.121	.126	.121
171cms.	63.5Kg	CO_2 Excretion	.168	.173	.175	.1720	.181	.176	.171	.196	.176=	.178	.172	.175	.179	.182	.189	.186
60 yrs.	M	Minute Ventilation	5.130	5.420	5.500	5.355	5.259	5.146	5.757	5.661	5.709	5.516	5.323	5.645	5.468	5.452	5.677	5.500
		Respiratory Rate	19.00	18.00	18.50	18.50	18.00	18.25	18.75	19.00	18.50	19.50	18.50	18.33	19.00	18.50	17.75	17.00
A.M.		Tidal Volumes	.471	.522	.519	.5042	.514	.494	.536	.524	.543	.493	.514	.537	.504	.518	.553	.569
1.75sq.m.		O_2 Uptake	.109	.122	.120	.1170	.115	.111	.125	.114	.114	.110	.113	.116	.123	.120	.123	.124
177cms.	60.5Kg	CO_2 Excretion	.166	.187	.186	.1797	.183	.168	.191	.176	.179	.187	.175	.182	.186	.190	.206	.189
44 yrs.	M	Minute Ventilation	3.457	3.516	3.589	3.531	3.428	3.589	3.501	3.501	3.439	3.454	3.293	3.307	3.205	3.527	3.483	3.424
		Respiratory Rate	13.25	14.25	13.25	13.58	12.75	14.00	13.25	13.50	13.25	13.25	12.75	13.00	13.50	14.00	13.50	13.50
A.W.		Tidal Volumes	.510	.499	.522	.5103	.531	.495	.507	.496	.515	.523	.493	.504	.497	.484	.502	.497
1.92sq.m.		O_2 Uptake	.113	.115	.116	.1147	.116	.118	.115	.114	.114	.115	.112	.114	.105	.112	.110	.112
171cms.	81Kg	CO_2 Excretion	.177	.178	.183	.1793	.177	.185	.180	.179	.180	.180	.172	.172	.167	.177	.176	.170
62yrs.	M	Minute Ventilation	4.648	4.618	4.618	4.633	4.449	4.281	4.465	4.159	3.930	4.174	4.276	4.230	3.879	4.031	4.169	3.985
		Respiratory Rate	18.75	18.00	18.76	18.50	18.00	16.75	16.50	16.25	15.33	15.25	16.75	16.75	15.00	15.50	17.00	16.75
J.C.		Tidal Volumes	.459	.469	.451	.4592	.452	.461	.485	.466	.472	.495	.480	.462	.462	.468	.447	.436
1.82sq.m.		O_2 Uptake	.122	.124	.123	.1230	.116	.117	.121	.113	.109	.113	.113	.109	.104	.114	.117	.108
175cms.	67.6Kg	CO_2 Excretion	.201	.205	.202	.2027	.196	.193	.201	.186	.178	.184	.191	.184	.169	.181	.187	.175

Table 29

Fractional Changes in Respiration, oxygen uptake, and carbon dioxide output after soluble phenobarbitone at 4, 9, 14 and 60 minutes following drug administration

Item	PERIOD OVER WHICH MEASURED			
	0 - 4'	0 - 9'	0 - 14'	0 - 60'
Ventilation	-.0224 ± .0091 (.0182)	-.0227 ± .0134 (.0268)	-.0145 ± .0124 (.0248)	-.0211 ± .0288 (.0576)
Respiratory frequency	-.0435 ± .0095** (.0190)	-.0479 ± .0113* (.0227)	-.0357 ± .0150 (.0300)	-.0478 ± .0253 (.0506)
Tidal volume	+.0171 ± .0118 (.0236)	+.0102 ± .0107 (.0214)	+.0157 ± .0049* (.0098)	+.0334 ± .0227 (.0454)
Oxygen uptake	-.0101 ± .0177 (.0353)	-.0174 ± .0162 (.0325)	-.0094 ± .0116 (.0232)	-.023 ± .0206 (.0413)
Carbon dioxide output	+.0126 ± .0175 (.0351)	-.0041 ± .0174 (.0348)	+.0018 ± .0112 (.0223)	-.0073 ± .0292 (.0584)

Table 30

Changes in $PaCO_2$ and pH after soluble phenobarbitone

Subject	Changes in $PaCO_2$		Changes in pH	
	Control (1)	Post Drug (2)	Control (1)	Post Drug (2)
A. Munro	39.00 ± .289 (.500)	36.17** ± .458 (1.586)	7.345 ± .003 (.006)	7.355 ± .002 (.008)
A.M.	39.50 ± 0 (0)	40.79 ± .387 (1.339)	7.327 ± .002 (.004)	7.328 ± .001 (.005)
J.C.	45.00 ± .289 (.500)	46.75 ± .392 (1.357)	7.398 ± .013 (.023)	7.391 ± .003 (.012)

(1) 3 control observations

(2) 12 post drug observations

Table 31

Changes in Ventilation and $PaCO_2$ and P_ACO_2 during sleep reported by various authors (1)

Source of Data	No. of Subjects	Fractional change in Total ventilation during sleep	Actual change in $PaCO_2$ and P_ACO_2	Fractional change in oxygen uptake (where given)
Robin, Whaley, Crump and Travis (1958)	13	-.2653 ± .0412 (.1486)	3.545 ± .455 (1.508)	-.2154 ± .0703
Birchfield, Sieker (3) and Heyman (1959	11	-.0872 ± .0281 (.0933)	4.091 ± .625 (2.071)	
Billow and Ingvar (2) (1961)	4	-.2316 ± .0154 (.0308)	2.00 ± .561 (1.122)	
Billow (1963) (2)	12	-.2059	2.1 ± 0.3	
Billow	12	-.2647	3.8 ± 0.4	

(1) Statistics calculated from reported data, except where otherwise indicated

(2) Statistical parameters not calculable from reported data

(3) Ventilation and $PaCO_2$ measured at different points in time

Table 32

State of Alertness following Drug Administration

Treatment Group	Onset of definite drowsiness (mean after injection)	+	++	+++	++++
5 mg/70 kg	17', 1', 3.5', 2', 6', 1'		2 (2.57)	3 (1.29)	1 (1.93)
10 mg/70 kg	2', 3', 4', 3', 3', 5', 3', 16', 1'		5 (3.86)	2 (1.93)	2 (2.89)
15 mg/70 kg	3', 1.5', 4', 10', 52', 15', 1', 1'	1	3 (3.86)	1 (1.93)	4 (2.89)
20 mg/70 kg	2', 4', 3.5', 5'		2 (1.71)	(.86)	2 (1.29)
Soluble phenobarbitone	36', 2', 3'	1		1	2

\+ Definite drowsiness throughout all or most of post drug period
++ More marked drowsiness; eyes closed from time to time for short periods
+++ Eyes closed most of the time for some part of post drug period
++++ Eyes closed most of the time for all or nearly all of post drug period.

Table 33

5 mg/70 kg group State of Drowsiness related to fall in ventilation and oxygen uptake

	M.W.	F.G.	G.R.	J.H.	W.B.	W.E.
Change in Ventilation	+.0118	+.0061	-.0447	-.0641	-.0715	-.0956
Change in state of alertness	+++	++	+++	++++	+++	++
Time of onset of drowsiness	1'	17'	3.5'	1'	2'	6'

	M.W.	G.R.	W.B.	W.E.	F.G.	
Change in oxygen uptake	-.0087	-.0113	-.o147	-.0427	-.0486	
Change in state of alertness	+++	+++	+++	++	++	
Time of onset of drowsiness	1'	3.5'	2'	6'	17'	

Table 33 (contd.)

10 mg/70 kg group — State of alertness related to fall in ventilation and oxygen uptake

	W.D.	A.W.	W.H.	J.N.	R.M.	A.McK.	I.S.	G.F.	W.J.
Change in ventilation	-.0207	-.0647	-.0702	-.0874	-.0915	-.1077	-.1118	-.1143	-.1397
Change in state of alertness	++	++++	++	++	++	+++	++	+++	++++
Time of onset of drowsiness	5'	2'	3'	3'	16'	3'	7.1'	4'	3'
	W.H.	I.S.	A.W.	W.D.	W.J.	A.McK.	G.F.	R.M.	
Change in oxygen uptake	+.0423	+.0119	+.0029	-.0013	-.0190	-.0286	-.0614	-.0951	
Change in state of alertness	++	++	++++	++	++++	+++	+++	++	
Time of onset of drowsiness	3'	2.1'	2'	5'	3'	3'	4'	16'	

15 mg/70 kg group State of alertness related to fall in ventilation and oxygen uptake

	J.McK.	J.C.	J.R.	A.M.	C.D.	A.N.	H.S.	J.P.	W.I.
Change in ventilation	-.0929	-.0955	-.1104	-.1263	-.1625	-.1732	-.2177	-.2288	-.2425
Change in state of alertness 1	+	++++	++	++	++++	++++	++	+++	++++
Time of onset of drowsiness	52'	4'	3'	10'	7.5'	15'	1'	0.5'	1'
	H.S.	C.D.	A.M.	J.C.	A.N.	J.McK.	J.P.	J.R.	W.I.
Change in oxygen uptake	+.0233	+.0203	+.0178	+.0147	-.0195	-.0290	-.0717	-.0726	-.0906
Change in state of alertness	++	++++	++	++++	++++	+	+++	++	++++
Time of onset of drowsiness	1'	7.1'	10'	4'	15'	52'	1.5'	3'	1'

Table 33 (contd.)

20 mg/70 kg group State of alertness related to fall in ventilation and oxygen uptake

	J.D.	C.R.	W.F.	J.R.
Change in ventilation	-.0961	-.1293	-.1581	-.2308
Change in state of alertness	++++	++	++	++++
Time of onset of drowsiness	3.5'	4'	5'	2'
	C.R.	J.D.	W.F.	J.R.
Change in oxygen uptake	+.0304	+.0141	=.0325	-.0487
Change in state of alertness	++	++++	++	++++
Time of onset of drowsiness	4'	3.5'	5'	2'