

3. The Use of Massive Doses of Digitalis.

4. The Relation of Digitalis Administration to Paroxysmal Ventricular Tachycardia in Man.

By

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OXYGEN THERAPY: INDICATIONS, PRINCIPLES, AND METHODS.

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ANOXÆMIA, or deficient oxygenation of the arterial blood, is a common condition and familiar to every practitioner. We propose to discuss briefly its production, the indications for treatment, and how therapy may be most efficiently carried out. A new method of oxygen administration for use by the practitioner is described, and at the same time we show the effect of the inhalation of oxygen on the amount present in the alveolar air when the gas is administered by various methods. This affords a means of comparing their efficiency and determining which are worthy of continued use both by the practitioner and in the hospital ward.

Signs and Symptoms of Anoxæmia.—As seen clinically, anoxæmia is often masked by other manifestations. In an acute form it is most commonly found in pneumonia, and here there are other factors acting which tend to overshadow it. The most pronounced of these is undoubtedly the profound toxæmia. Anoxæmia also occurs in an acute form in asphyxia, but here again its presence is complicated by the additional factor of carbon dioxide retention. Acute oxygen-want in itself, then, is comparatively rare and there are practically always other factors at play, e.g. deficiency or excess of carbon dioxide. The clearest picture of the condition is found in mountain sickness and aviators have frequently had opportunities of making themselves familiar with its effects. The

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classical description of the condition is given by Tissandier in an account of a balloon ascent and quoted by Paul Bert. Haldane has described fully the clinical condition.

It is in pneumonia, however, that the practitioner meets acute oxygen-want of a most serious nature. As pointed out above, in this disease the condition is masked by the toxæmia from which the patient also suffers and this perhaps helps to explain why the part played by lack of oxygen tends to be neglected from the therapeutic point of view. The signs and symptoms are well known and may be studied in any case of severe lobar pneumonia. The respirations increase in rate and change in type. Gradually they assume the rapid, shallow type and are further embarrassed by the pleural pain which is so disturbing to the patient. The appearance alters; at first flushed, the face assumes an anxious expression and cyanosis appears about the cheeks, lips, ears, and fingers. The pulse rate rises, the blood pressure tends to fall and with this the patient's chances of recovery are frequently diminished further by restlessness, and later delirium. The limbs feel heavy, weak, and powerless, and occasionally twitchings of the facial muscles are noted. It is insufficiently realised of how great benefit oxygen administered efficiently and in sufficient quantity may be to such a case.

Causes of Oxygen-Want.—These are numerous and we propose to group them under three headings.

(1) Where there is insufficient partial pressure of oxygen in the inspired air—e.g. mountain-sickness, or where through abnormality or damage of the respiratory tract, e.g. tumours, laryngeal obstruction, pneumonia—the arterial blood does not receive its normal load of oxygen.

(2) Circulatory States. Here, though the amount of oxygen in the arterial blood may be within normal limits, the circulation is so slowed that the tissues do not receive their normal amount of oxygen. Both these factors (1) and (2) may be operative together, as in a decompensated cardiac case with pulmonary oedema.

(3) Alterations in the blood whereby it is rendered incapable of carrying the normal load of oxygen—e.g. anæmia and carbon monoxide poisoning. Finally, alterations in the tissues which handicap them in making use of the normal amount of oxygen offered them—e.g. in certain types of poisoning, notably with cyanides.
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Most of the causes of oxygen-want may thus be grouped together, but we would specially confine our remarks to acute anoxæmia, and cannot do better than discuss its production in pneumonia, as this is the type which most commonly calls for treatment. In all cases of pneumonia and broncho-pneumonia there is a greater or less degree of oxygen unsaturation of the arterial blood, as has been shown by Stadie and Meakins. Normally the blood is 95 per cent. saturated, and in pneumonia this figure falls in proportion to the severity of the anoxæmia. Since the inspired air contains the normal amount of oxygen, we have therefore to explain how the oxygen of the arterial blood is decreased in amount. In pneumonia there are at least three factors which cause this. The first is that blood coming from a consolidated lobe will remain venous in character owing to the fact that there is little or no ventilation of its alveoli. The second is that in the early stages there is exudation into the alveoli which hinders the passage of oxygen from the alveolar air to the capillaries. The third is that owing to shallow respiration, and therefore unequal ventilation of different parts of the lungs, the blood from the poorly ventilated parts will be poorly oxygenated and will diminish the oxygen saturation of the mixed arterial blood. Once established, oxygen-want tends to perpetuate itself, for it has been shown by Haldane, Meakins, and Priestley that rapid shallow breathing is in itself both a cause and a result of anoxæmia. A vicious circle may thus be established.

Effect of Anoxæmia.—It is to be recognised that this condition, especially in cases of pneumonia, begins gradually and insidiously, and tends to become progressively worse. By the time the respirations have reached 25 to 30 per minute, and more particularly when the shallow form of respiration is established, it may be assumed that the oxygen saturation of the blood is definitely below normal. It has been shown by several authors (see Lundsgaard and Van Slyke*) that in the absence of circulatory stasis, cyanosis does not commence to be apparent until the oxygen saturation of the arterial blood has fallen to 80 or 85 per cent. Even before this stage is reached damage may be done to the myocardium, central nervous system, or excretory organs. The shallow breathing steadily increases in rate and the oxygen saturation of the blood continues to fall. Delirium further exhausts the patient.

and the oxygen-want lowers his resistance to the pneumococcal toxins. Increasing tachycardia and falling blood pressure are of ominous prognostic significance. At present there is little definite evidence regarding the rôle of the initial slight anoxaemia in bringing about these severe symptoms, but it is probable that lack of oxygen is of great importance. Observations by Haldane and his associates at Pike's Peak on the pulse-rates and blood pressures\(^6\) led to the following conclusions: "It is probable that a considerable element of vasomotor derangement is involved in mountain-sickness and that even in persons fairly well acclimated the vasomotor equilibrium is less perfect than at sea level." As the myocardium fails the blood pressure falls, the heart tends to dilate, and the efficiency of the circulation is generally impaired. Under these circumstances a dangerous vicious circle is initiated, for as the arterial unsaturation increases so the myocardium and the circulation are further embarrassed, adding the further complication of tissue oxygen-want resulting from impaired circulation.

**The Indications for Treatment.**—Obviously the outstanding indication in such cases is to break the vicious circle. This can only be accomplished in one way, and that is by giving oxygen in such a manner that the arterial saturation is never allowed to fall. It is common knowledge that, in the past, clinicians were disposed to dispense with oxygen as a useless therapeutic agent, and even still, so strong is tradition in medicine, it is sometimes taught with great conviction that oxygen is of no value in pneumonia. "Convictions," as Sir Berkeley Moynihan has said, "often masquerade as truths, and the strength of a man's conviction may display only the defect or weakness of his knowledge." Until the war, the gas had fallen more or less into disrepute, because until then, the factors in the production of anoxaemia were little understood, and no practical and efficient manner for everyday use had been devised for treating it. Even to-day there is no therapeutic procedure more unsatisfactorily carried out. In selected cases oxygen is a life-saving remedy if used intelligently and in an efficient manner. There is considerable clinical evidence to indicate that if oxygen were used more frequently and after the manner described below, the mortality from pneumonia could be reduced, the severity of the symptoms markedly lessened, and a speedier termination of the infective process assured.
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As a general rule, when oxygen is used, the amount given is far too small; it is not administered continuously, or, more commonly, its use is reserved until the patient is in extremis. Moreover, the actual administration is too often left entirely under the care of a nurse or attendant who is unskilled in the method and unaware of the objects in view.

The object in giving oxygen is so to increase the partial pressure of the gas in the lung alveoli, and thereby the oxygen saturation of the blood, that anoxæmia cannot develop—i.e., to get that volume of oxygen into the lungs which will completely abolish, or better, prevent cyanosis. As Meakins has shown the aim should be to forestall and prevent cyanosis in all cases of pneumonia, for, if oxygen therapy be delayed until the onset of cyanosis, the patient will have already sustained damage to the central nervous system and myocardium. There is abundant evidence that delirium and circulatory failure in pneumonia can be prevented by the early and efficient use of oxygen; but, if these be allowed to appear or continue for a few hours, oxygen therapy often fails to relieve them. Meltzer realised this and suggested that failure of oxygen therapy might frequently be due to its use being too long delayed.

"It seems justifiable to assume that the period of definite cyanosis is preceded by a more or less long period, during which the capacities for taking up oxygen . . . are gradually getting impaired; and it is further justifiable to assume that during this pathologic period the insufflation of oxygen may be capable of restoring these capacities to their normal extent more frequently and efficiently than during later stages. The early insufflation may thus be the means of preventing the disease from reaching the stage of cyanosis." We have frequently seen cases of pneumonia where oxygen failed to relieve delirium after the latter had been present for several hours. On the other hand oxygen administration seldom fails to relieve slight delirium or the agitated restlessness so commonly present in pneumonia patients, provided it be carried out efficiently as soon as these symptoms become manifest.

The Effect of Oxygen Administration.—It has been shown above that there are at least three factors in the production of anoxæmia in pneumonia. When the stage of hepatisation has been reached, ventilation practically ceases so far as the affected lobe is concerned, and it is not likely that the administration of oxygen will have any appreciable effect upon
the blood coming from a consolidated lobe. Where, however, there is exudation into the alveoli, together with some ventilation, an increased percentage of oxygen in the alveolar air will facilitate the passage of oxygen into the blood of the alveolar capillaries. Also if the mean alveolar oxygen percentage be increased, the effect of poorly ventilated portions of the lungs upon the oxygen saturation of the mixed arterial blood will be diminished. Moreover, a higher oxygen percentage in the well-ventilated alveoli will increase the amount of oxygen in simple solution in the blood plasma, so that in spite of poor ventilation in parts of the lungs and non-ventilation of the consolidated lobes, the oxygen saturation of the mixed arterial blood will be increased. By continued administration the oxygen saturation of the arterial blood can be kept at or near the normal level, and the vicious circle established by lack of oxygen can thereby be broken. When this has been accomplished cyanosis disappears, the pulse rate falls by 8 to 12 beats per minute, the patient assumes a more comfortable aspect, and a brighter outlook is assured. The bodily resources are then reinforced to fight a single enemy and the effects of the toxaemia are minimised. It would seem that in pneumonia active immunity can be established even with a severe infection, provided the patient be tided over and prevented from succumbing to acute oxygen-want. All clinicians who are accustomed to use oxygen by an efficient and adequate method are familiar with the fact that even desperate cases of pneumonia can often be tided over by this means.

The Principles in Oxygen Therapy.—The first essential is to commence oxygen treatment early and to have at hand an efficient apparatus for its continuous administration. Cyanosis must be prevented, and to do this the patient must receive a definite volume of oxygen into the lung alveoli per minute. It is necessary to raise the percentage of oxygen in the alveolar air considerably above the normal level in order to give the oxygen a greater *vis a tergo* in its passage through the damaged or thickened alveolar epithelium. Moreover, it is only by this means that the blood from the well-ventilated parts of the lungs can be given sufficient oxygen in combination, and in simple solution so as to make up for the deficient oxygenation of the blood from non-ventilated lobes, and thus provide a mixed arterial blood within the normal limits of oxygen saturation. Clinical studies have shown that adults suffering from
pneumonia breathe between 10 and 15 litres of air per minute, as compared with the 5 to 10 litres respiratory minute volume of normal resting individuals. According to the level of the oxygen unsaturation of the blood, so it is necessary to increase the percentage of oxygen in the alveolar air. With the respiratory volume of 10 to 12 litres per minute the addition of 3 litres of oxygen per minute would raise the oxygen percentage in the inspired air to approximately 45, and in the alveolar air to approximately 35, the normal value being from 14 to 15 per cent. Meakins has shown that the administration of oxygen by the Haldane apparatus at a rate of between 2 and 3 litres per minute was sufficient to raise the percentage oxygen saturation of the arterial blood from 80 to the normal 95 or even above. This increase was associated with marked clinical improvement. Obviously the increase in the oxygen saturation of the blood must depend upon the increased oxygen percentage in the inspired air, and this in turn on the ratio between the volume of air inspired (i.e., the respiratory minute volume) and the volume flow of oxygen per minute. In any sound method for oxygen treatment it is necessary then to adapt the flow of oxygen to the patient's minute volume. A flow of 3 litres of oxygen per minute may be insufficient to abolish anoxæmia in severe cases of pneumonia with extensive consolidation, high respiratory rate, and greatly increased minute volume of respiration. Such cases of pneumonia may have an arterial saturation much below 80 per cent. One of us had opportunities of investigating cases of this type before and during treatment in the oxygen chamber at the Hospital of the Rockefeller Institute, New York. One patient while breathing ordinary room air had an arterial oxygen saturation of only 50 per cent. When placed in the oxygen chamber and inspiring air containing 39 per cent. of oxygen, the arterial oxygen saturation rose to 75 per cent., while with 58·5 per cent. of oxygen in the inspired air it rose to only 80 per cent. after several hours, a degree of anoxæmia indicative of grave danger in a case of pneumonia. While such severe cases are unusual in this country, nevertheless it is evident from the above figures that in some cases it may be necessary to obtain an inspired air consisting of almost pure oxygen in order to abolish completely the anoxæmia. In our opinion even in those cases with an arterial oxygen saturation of 80 per cent., it seems advisable to regulate the flow of oxygen
so as to give initially a very high percentage in the inspired air and thereby abolish the anoxæmia rapidly (i.e., a volume of pure oxygen per minute which will practically equal the patient's respiratory minute volume). After this has been accomplished the rate of flow of oxygen may be retarded to such a degree that the tendency to anoxæmia is kept under control and the oxygen saturation of the blood within normal limits. The clinical evidence of this consists in the complete abolition of cyanosis, the fall in pulse rate, and the subjective improvement. At this point a few words must be said regarding the necessity for continuous or almost continuous administration of oxygen. The ability of an individual to store oxygen in his blood and tissues is practically negligible. Less than half a litre of additional oxygen can be stored in the lungs, blood, and tissues, and this, with the increased metabolism of fever, would be sufficient to supply the demands for only a very brief period. Clinical evidence of this is afforded by the rapid return of cyanosis and increasing pulse rate when the oxygen administration is stopped.

Methods of Oxygen Therapy.—From what has been said above, it can at once be seen that any apparatus designed for administering oxygen to a patient should fulfil certain practical requirements. The most important of these from a therapeutic point of view is in regard to the amount of oxygen reaching the lung alveoli per minute. Taking the oxygen percentage of the alveolar air as an indication, we have endeavoured to compare various methods of administration, the most efficient method being that which, for a given rate of oxygen flow, in a given subject produces the highest percentage of oxygen in the alveolar air, for the higher the partial pressure of oxygen in the alveoli, the more is the blood likely to become completely saturated. It is essential also that the apparatus be provided with a reducing valve, whereby a steady flow of oxygen from the cylinder is maintained even when the latter is almost empty. It is also necessary to have some simple means of reading the rate of delivery of oxygen to the patient. If a face mask be employed, then it must be light, easily adjusted, and close-fitting, to avoid waste of oxygen into the surrounding atmosphere. Furthermore, it is desirable that a reliable apparatus should be so adapted that the percentage of oxygen in the inspired air can be varied according to the patient's requirements, Different cases of pneumonia require a different rate of flow,
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and an efficient apparatus must be able to supply varying demands for oxygen. As in the case of other substances used for therapeutic purposes, the dose of oxygen must be known and be adequate to produce the desired effect. Economy in the use of oxygen demands serious attention. Whatever method of administration be employed the patient must benefit to the full by the oxygen offered to him and waste must be cut down to a minimum. The most important means of avoiding waste of oxygen is to secure an intermittent flow so that the gas may be conserved during expiration.

With these essentials before us it is well to compare some methods of oxygen administration in common use at the present time, with a view to arriving at definite conclusions as to which, if any of these, is worthy of a place in practical therapeutics.

Perhaps the most primitive and certainly the most useless is the so-called "tube and funnel." This method proved absolutely valueless to our grandparents, yet it is still to be seen in hospital wards. The private practitioner seldom uses it. As usually employed, oxygen is bubbled at a ridiculously slow rate through water and delivered by a funnel in more or less close proximity to the patient's face. This method requires the constant attendance of a second person and, even if oxygen could be delivered into the alveoli at a sufficiently high partial pressure, it is unsuited for continuous administration. Those in charge of such an apparatus always appear reluctant to increase the rate of flow to an extent which would have any chance of benefiting the patient. We have found that oxygen bubbling at the rate of four bubbles a second from a tube 0.5 cm. in bore corresponds to a rate of delivery of 0.27 litre per minute. This rate, far above that usually employed, would have no appreciable effect upon a patient suffering from anoxæmia. An analysis of the alveolar air showed only 15.24 per cent. of oxygen after breathing for five minutes at this rate of flow with a funnel of 4 in. diameter held 2 1/2 in. distant from the tip of the nose. At a rate of flow of 2 litres a minute with the funnel touching nose and chin we were able to increase the percentage of oxygen in the alveolar air to 26.7. This figure is of little or no value, and it is safe to say that there could be no better means devised of wasting oxygen. This method has absolutely no value in practical therapeutics.

To Adrian Stokes is generally given the credit of having
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devised the method of inserting a rubber tube along the floor of the nose whereby a steady flow of oxygen is delivered into the naso-pharynx. This method was first used in France on "gassed" men, and had the advantage that several cases could be treated at once and from the same cylinder. It gives fairly good results in some cases. Later it has been used in the clinic and has proved of value in infants and children. Geoffrey Bourne has adapted it for these cases by using a rubber catheter, size 6, smeared with 1 per cent. cocain ointment and held in position by an aluminium rod attached to a forehead band. In these cases it has been found to give excellent results if the anoxæmia be treated early before the arterial oxygen saturation has had time to fall greatly. As an emergency method it can be made use of readily in adults. But when used with a Wouff's bottle whereby the oxygen is made to bubble through warmed water, then in our experience the temptation is to have too slow a rate of flow. On the other hand a sufficiently high minute flow of oxygen—say 6 to 8 litres—is distinctly annoying to the patient and gives rise to great discomfort in the naso-pharynx. Also in those cases which demand a high percentage of oxygen in the alveolar air, as the majority of cases of pneumonia do, this method, while of great value in infants, is unable to supply the demand. Owing to there being no means for conserving the gas during expiration, this method wastes at least half of the oxygen. Analyses of the alveolar air after using this method at rates of flow of 2 and of 8 litres per minute in a subject whose respiratory minute volume was 6.23 litres showed respectively 27.6 and 43.4 per cent. of oxygen. The latter rate of flow was, however, decidedly uncomfortable.

Macleod states that by having the catheter in one nostril and closing the other with the finger during each inspiratory act he was able slightly to increase the efficiency of the method.

A method of oral insufflation of oxygen has been described by Meltzer. Macleod states that by this method and with the nose clamped he has been able to obtain an oxygen percentage of 85 in the alveolar air. We have no personal experience of this method, but it appears to have one very obvious disadvantage, namely, that the valve controlling the intermittent oxygen flow must be worked by hand at a rate corresponding to the patient's respiratory rate.

J. S. Haldane in 1917 published a description of a simple
method for oxygen administration in which the gas was automatically conserved during expiration. This method was a very great advance on all previous methods, and has been a very important means of showing the great therapeutic value of oxygen efficiently administered. We would refer the reader to the original publications for a detailed description but, in so far as our own method described below is essentially a modification of the Haldane method, it is necessary to give a brief résumé of it. Oxygen is delivered to a face mask which has in addition an extra air orifice partly occluded by a loose rubber flap. This flap creates a slight negative and positive pressure during inspiration and expiration respectively. During expiration the positive pressure is sufficient with moderate rates of oxygen flow to close a small mica valve and direct the stream of oxygen into a small bag. During inspiration the small amount of negative pressure is sufficient to open the mica valve and suck the stream of oxygen, together with what has accumulated in the bag, into the mask. The partially occluded orifice in the mask allows of the addition of sufficient room air to make up a complete inspiration. It also allows of expiration into the room air. The small amount of resistance necessary to ensure the intermittent supply of oxygen to the mask is entirely negligible. The cylinder head attachment for this apparatus consists of a reducing valve, and a calibrated regulating valve which is marked in litres per minute. For low rates of oxygen flow (up to one-third or slightly more of the respiratory minute volume) it is unlikely that any apparatus can be devised which will be more efficient than the Haldane. In our earlier experiments we used the light "field pattern" of Haldane apparatus. This pattern, which was devised to meet the emergencies of war service, is in certain respects unsatisfactory for general use. The bag and valve for conserving oxygen during expiration are attached to the mask, rendering the latter more clumsy and forming a source of annoyance to the patient. The bag interferes with expectoration, is too small, perishes rapidly, and often leaks even in a perfectly new apparatus. These are minor defects and are absent in the larger "hospital type" of apparatus. The hospital type differs from the field pattern in that the bag and valve for conserving oxygen during expiration, instead of being attached to the mask, form part of the cylinder head attachment. The bag is of stronger fabric and more capacious, and the regulating
valve is calibrated for rates of flow up to 10 litres per minute—5 litres being the maximum in the majority of “field pattern” apparatuses. With the Haldane apparatuses the administration of oxygen is a simple matter. After the mask has been adjusted to the patient's face it is customary to deliver oxygen at a rate of flow varying between 2 and 3 litres per minute. This is as a rule sufficient to abolish all signs of anoxæmia and to raise the oxygen saturation of the arterial blood to normal or even above. When such a rate of flow is all that is required to abolish anoxæmia the mask is economical in its use of oxygen and none is wasted. On the other hand certain severe cases of pneumonia demand a higher percentage of oxygen than can be economically supplied by the Haldane apparatus. Where the rate of oxygen flow was half the total air breathed per minute the alveolar oxygen percentage rose to 50 per cent., but when the oxygen flow corresponded to the respiratory minute volume it rose to 67 per cent. By doubling the rate of flow of oxygen, it was therefore only possible to increase the alveolar oxygen by a further 17 per cent. Up to half the respiratory minute volume this is a most efficient means of administering oxygen, but above this proportion the efficiency of the method rapidly declines, an increasing proportion of the oxygen passing to the outflow opening during expiration, and thus being of no use in raising the alveolar oxygen percentage.

Oxygen chambers are in use in certain large hospitals in this country and America, and, while they have several obvious advantages over the commoner means of administrating oxygen, there are factors which would seem to outweigh these. They are expensive to build, require highly skilled supervision when in use, and necessitate the most elaborate precautions against fire. Moreover, in even the best chambers at present in existence it is difficult, if not impossible, to obtain an atmosphere containing more than 60 per cent. of oxygen, and this, as we have shown above, may be insufficient in certain cases. The average case of pneumonia can certainly be well and continuously treated for several days in an oxygen chamber, without the use of a mask or other device; but the number of cases so treated at one time is strictly limited, and it is improbable that oxygen chambers will ever come into general use.

New Outfit for Oxygen Administration.—In designing a new oxygen administration outfit we have had several objects
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in view. So far as possible our aim has been to produce an apparatus of maximum efficiency both at high and low rates of flow, and to provide at the same time an easy means of determining the ratio of oxygen flow to the total volume of air breathed per minute. By this means it is possible to estimate roughly the percentage of oxygen present in the patient's alveolar air, and to abolish completely all signs of anoxæmia. This in itself gives a measurement of the severity of the anoxæmia, and forms a standard rate below which the flow of oxygen should not be allowed to fall.

The cylinder head attachment consists of a pressure gauge, reducing valve, and a regulating tap. This comprises one fixture which is screwed on to the head of the oxygen cylinder. The pressure gauge records in atmospheres (the usual standard of a full cylinder being 120 atmospheres pressure). The oxygen passing from the outflow tube is led through a flow meter to a rubber bag of about 4 to 5 litres capacity, where it accumulates. From the bag a tube of wide bore leads the oxygen to a glass wash-bottle containing water. The lead-in tube dips just under the surface of the water and thus acts as a valve. Thus we have adopted the principle of the Haldane apparatus whereby oxygen is conserved during expiration. The type of valve, i.e., the Müller water-valve—which we have adopted possesses an additional advantage, namely, that the flow of oxygen can be observed. From the bottle a tube of similar bore (about $\frac{1}{2}$ in.) runs to a specially designed mask. This mask differs from those described above in that it is possible to regulate the amount of room air inspired by the patient. This is accomplished by having an expiratory valve, a tube leading in the oxygen, and also an inspiratory orifice of variable size to admit extra air. With the latter completely closed, the demand made by inspiration can be satisfied only from the oxygen inflow, which must be so adjusted as exactly to satisfy this demand. How this may be done is described below. It is possible thus to determine the minute volume of respiration, as this quantity can be read from the flow meter in litres per minute.

With each inspiration, the negative pressure produced draws oxygen from the bag to the lungs, and the gas can be seen bubbling through the water-valve. On expiration, the positive pressure is sufficient to open the expiratory valve on the front of the mask and the patient expires to the outside air. At the same time this pressure is transmitted along the wide
tube leading to the water-valve, and should be sufficient to stop all bubbling (and therefore waste of oxygen) during expiration. During this time oxygen accumulates in the bag in readiness for the next inspiratory act. When the flow of oxygen is accurately adjusted to the patient's minute volume of respiration, then bubbling takes place only during inspiration, and the bag in which the oxygen accumulates during expiration never completely fills. If the rate of oxygen flow be higher than the subject's minute volume of respiration, the result is that the bag overfills and the gas escapes through the water-valve and causes at first bubbling for a short time during the latter part of expiration, and later continuous bubbling. This results in a continuous oxygen flow which, apart from being disturbing to the patient, is also wasteful. If the rate of oxygen flow be too small, then the bag gradually empties and bubbling is reduced to a minimum during inspiration. The patient soon becomes aware of this and will not tolerate the mask.

Mention has been made of an adjustable inspiratory orifice on the mask which communicates with the outside air. This, as pointed out above, may be closed, in which case the patient demands a flow of oxygen at least equal to his minute volume of respiration. On opening the orifice extra air may be inspired, but the tendency is for the negative pressure set up by each inspiratory act to be more readily satisfied by the accumulated oxygen than by extra air. This device constitutes the essential principle of the new mask, for by this means it is possible to adjust the amount of extra air inspired to the rate of oxygen flow per minute. With the orifice wide open it is possible for the patient to breathe comfortably without any oxygen. With the orifice closed the flow of oxygen must be made sufficient to supply completely the demand of each inspiratory act. Between these two extremes it is possible to vary the ratio between the minute volume of oxygen and the amount of room air inspired. The optimum amount of oxygen necessary for the patient may thus be found, and the additional air necessary to complete each inspiratory act is admitted by varying the size of the orifice. If too much air be allowed to enter the mask with each inspiration, then bubbling in the water-valve gradually decreases in amount, oxygen tends to accumulate in the bag and, more important, cyanosis and other evidences of anoxæmia will assuredly give rise to doubts as to whether the
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patient is receiving enough oxygen. The temptation is to allow too little air to enter the mask in proportion to the flow of oxygen. In such a state inspiration becomes an effort to the patient. He has to fight for the necessary volume of room air to complete each inspiratory act and gradually the bag is completely emptied. To a pneumonia patient such a state of affairs would be intolerable, and when this stage is reached he will quickly remove the mask from the face. The remedy consists either in increasing the rate of oxygen flow, or opening further the inspiratory orifice on the front of the mask so that sufficient air is allowed to enter. In practice it is well to commence treatment with a flow of oxygen approximately equal to the minute volume of respiration, say 10 litres per minute. When the bag is more than half full the mask with the extra air orifice closed is accurately adjusted to the face. The patient will now find that his deepest inspiratory effort can be completely satisfied by an immediate and copious flow of oxygen. By watching the water-valve to see that bubbling takes place only during inspiration, and noting that the bag neither completely empties nor overflows, it is easy to adjust the flow of oxygen to the patient's requirements. When this has been accomplished a reading of the flow meter gives approximately the patient's minute volume. After a few seconds at this rate of flow, if the oxygen-want is due to oxygen unsaturation of the arterial blood, all signs of anoxæmia will disappear. The oxygen flow may now be retarded to whatever may be necessary to hold the symptoms of anoxæmia in abeyance, and the extra air orifice opened in order that the necessary volume for each inspiratory act may enter the mask.

Patients are sometimes inclined to object to the continuous use of an oxygen mask, and to obviate this it is an advantage to have the mask made of some light metal—e.g. aluminium, and cut so that it is easily adaptable to the face. Leakage round the sides of the mask may be a great source of inefficiency and is reduced to a minimum by the presence of the usual inflatable rubber cushion. A broad band of elastic webbing which passes round the head secures the mask to the face, and it has been found of advantage to have this readily detachable from the mask, so that the patient may himself uncover his mouth in order to expectorate, or during violent bouts of coughing. The mask may be then securely replaced by the patient himself. Notwithstanding these attentions to
make the mask more convenient and comfortable in use, the best of patients tend to tire, and, in order to maintain con-

FIG. 1.—Diagram of New Oxygen Outfit.

The Outfit consists of three parts:

(1) Attachment for head of cylinder (A). This consists of a pressure gauge (B), reducing valve (C), and flow regulator (D). The gas escaping from the cylinder is led by the tube (E) to

(2) A box, where it passes through the flow-meter (F), and tends to accumulate in the bag (G). The oxygen then enters the water valve (I) by the wide lead-in tube (H). The water valve stands inside a vessel (J), into which hot water may be poured in order to warm the oxygen. The oxygen is then led by wide corrugated rubber tubing (K) to

(3) A face mask (L) or a "forked nasal tube" (O). The mask is of special design and has an expiratory valve (N) and an extra-air orifice (M). It is attached to the head by a broad band of elastic webbing. The forked nasal tube is held in position by a forehead band. In each case the oxygen delivery tube passes from behind the patient's head so that the patient is enabled to move freely without kinking or lying on the tube.

continuous administration, it is well to be able to substitute some method other than the mask. To do this we have devised a nasal tube, one end of which is attached to the tube from the
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water-valve. On the other end are two short curved tubes of equal bore, one of which is inserted just inside each nostril. They must fit loosely so as to permit a free air way round about them. This forked tube is held in position by an elastic head band. With such an apparatus it is possible, with a flow of oxygen equal to about half the respiratory minute volume, to raise the percentage of oxygen in the lung alveoli to approximately 50 per cent. This method is of use in the less severe cases of pneumonia, where the patient may object to the use of a mask and is able to breathe freely through the nose with the mouth closed. Even with a moderate amount of oral respiration, such as may occur during sleep, this method works efficiently with an oxygen flow up to one third of the respiratory minute volume. Such an amount of oxygen is of great service in overcoming mild and even moderate degrees of anoxaemia, and we have found that the continuous administration of oxygen is rendered much more agreeable to the patient by using the mask and forked tube alternately.

The oxygen outfit described above is being made for us by Messrs Siebe, Gorman & Co., 187 Westminster Bridge Road, London, S.E. 1, and consists of three essential parts: (1) An attachment for the head of the oxygen cylinder; (2) a box containing the water-valve and oxygen bag and flow meter. This may be conveniently hung on the back of the patient’s bed or on the wall above his head. (3) A mask and set of “forked-tubes” of different sizes. The whole outfit may be stored in the box and is always ready for use. A diagrammatic sketch of the apparatus is shown in Fig. 1.

Comparison of the Efficiency of Various Methods.—Knowing the rate of flow of oxygen delivered per minute and the subject’s respiratory minute volume, it is possible to calculate the maximum percentage of oxygen in the alveolar air. This has been done for different values and the results are given in Table I. In estimating the efficiency of any apparatus we have compared the increase of oxygen percentage found in the alveolar air after five minutes’ use of the method, with the calculated maximum increase theoretically obtainable. By this means we have determined the percentage efficiency of each method. The findings are given in Table II.

Besides affording a means of comparing one method with another, this table also demonstrates the percentage efficiency of any given method with different ratios of oxygen flow to
respiratory minute volume. For instance, it can be seen that the Haldane apparatus is much superior to either the “tube and funnel” or the nasal catheter for all ratios, but at the same time the efficiency of the Haldane method tends to decline as the rate of flow of oxygen approaches the patient’s respiratory minute volume. The new method described above is very efficient at both high and low rates of flow, when the mask is employed, and the table demonstrates that the “forked nasal tube” while not so efficient at a high ratio as at a low one, is much superior to the nasal catheter or “tube and funnel” methods.

**TABLE I.**

Showing maximum percentage of oxygen obtainable in the alveolar air at various minute volumes of respiration when oxygen at different rates of flow is added to the inspired air. E.g. A subject breathing at six litres per minute, and with three litres of oxygen per minute added to the inspired air, should have an alveolar oxygen percentage of 54.

<table>
<thead>
<tr>
<th>Respiratory Minute Volume in Litres.</th>
<th>3.</th>
<th>4.</th>
<th>5.</th>
<th>6.</th>
<th>7.</th>
<th>8.</th>
<th>9.</th>
<th>10.</th>
<th>11.</th>
<th>12.</th>
<th>13.</th>
<th>14.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Litres per Minute Oxygen Flow.</td>
<td>1</td>
<td>41</td>
<td>34</td>
<td>30</td>
<td>28</td>
<td>26</td>
<td>24</td>
<td>23</td>
<td>22</td>
<td>21</td>
<td>21</td>
<td>19</td>
</tr>
<tr>
<td>2</td>
<td>67</td>
<td>54</td>
<td>46</td>
<td>41</td>
<td>37</td>
<td>34</td>
<td>32</td>
<td>30</td>
<td>29</td>
<td>28</td>
<td>27</td>
<td>26</td>
</tr>
<tr>
<td>3</td>
<td>94</td>
<td>74</td>
<td>62</td>
<td>54</td>
<td>48</td>
<td>44</td>
<td>41</td>
<td>38</td>
<td>36</td>
<td>34</td>
<td>33</td>
<td>32</td>
</tr>
<tr>
<td>4</td>
<td></td>
<td>94</td>
<td>78</td>
<td>67</td>
<td>60</td>
<td>54</td>
<td>50</td>
<td>46</td>
<td>43</td>
<td>41</td>
<td>39</td>
<td>37</td>
</tr>
<tr>
<td>5</td>
<td></td>
<td></td>
<td>94</td>
<td>80</td>
<td>71</td>
<td>64</td>
<td>58</td>
<td>54</td>
<td>50</td>
<td>47</td>
<td>43</td>
<td>43</td>
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<tr>
<td>6</td>
<td></td>
<td></td>
<td></td>
<td>94</td>
<td>82</td>
<td>74</td>
<td>67</td>
<td>63</td>
<td>58</td>
<td>54</td>
<td>51</td>
<td>48</td>
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<tr>
<td>7</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>94</td>
<td>84</td>
<td>76</td>
<td>70</td>
<td>65</td>
<td>61</td>
<td>57</td>
<td>54</td>
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<td>8</td>
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<td></td>
<td>94</td>
<td>85</td>
<td>78</td>
<td>72</td>
<td>67</td>
<td>63</td>
<td>60</td>
</tr>
<tr>
<td>9</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>94</td>
<td>86</td>
<td>79</td>
<td>74</td>
<td>69</td>
<td>65</td>
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<td>10</td>
<td></td>
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<td>86</td>
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<td>87</td>
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<tr>
<td>12</td>
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<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>94</td>
<td>87</td>
<td>82</td>
</tr>
</tbody>
</table>

**Cost of Oxygen Administration.**—In the absence of a clinically satisfactory method of utilising liquid oxygen, the supply of oxygen depends upon its storage at high pressure in bulky cylinders. As used by physicians, these are generally of 20 to 40 cubic feet capacity and being of such small size they are uneconomical for hospital use, but owing to their portability are necessary in private practice. A cylinder of 20 cubic feet capacity delivering oxygen at 3 litres per minute would be emptied in three hours. For hospitals and nursing homes we recommend the use of large cylinders of 100 cubic feet capacity when filled to the standard pressure of 120 atmos-

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TABLE II.
Showing percentage efficiency of different methods of oxygen administration at various ratios of oxygen flow to respiratory volume per minute.

<table>
<thead>
<tr>
<th>Method</th>
<th>Rate of O₂ Flow in Litres per Minute</th>
<th>Respiratory Minute Volume in Litres</th>
<th>Ratio of O₂ Flow to Respiratory Minute Volume</th>
<th>Calculated Alveolar O₂ per cent. (see Table 1.)</th>
<th>Observed Alveolar O₂ per cent.</th>
<th>Efficiency expressed as Percentage</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tube and funnel</td>
<td>2.0</td>
<td>6.2</td>
<td>0.32</td>
<td>49</td>
<td>27</td>
<td>49</td>
<td>Funnel touching nose and chin.</td>
</tr>
<tr>
<td></td>
<td>4.0</td>
<td>6.1</td>
<td>0.65</td>
<td>67</td>
<td>29</td>
<td>29</td>
<td>Funnel edge 2&quot; away from tip of nose.</td>
</tr>
<tr>
<td></td>
<td>8.0</td>
<td>6.2</td>
<td>1.29</td>
<td>94</td>
<td>47</td>
<td>41</td>
<td>Funnel touching nose and chin.</td>
</tr>
<tr>
<td>Nasal catheter</td>
<td>2.0</td>
<td>6.2</td>
<td>0.32</td>
<td>49</td>
<td>28</td>
<td>53</td>
<td>...</td>
</tr>
<tr>
<td></td>
<td>4.0</td>
<td>6.7</td>
<td>0.60</td>
<td>62</td>
<td>33</td>
<td>40</td>
<td>Great discomfort at this rate of flow.</td>
</tr>
<tr>
<td></td>
<td>8.0</td>
<td>6.2</td>
<td>1.29</td>
<td>94</td>
<td>43</td>
<td>37</td>
<td>...</td>
</tr>
<tr>
<td>Haldane apparatus</td>
<td>2.0</td>
<td>9.5</td>
<td>0.21</td>
<td>31</td>
<td>32</td>
<td>100 (+)*</td>
<td>...</td>
</tr>
<tr>
<td></td>
<td>3.0</td>
<td>8.7</td>
<td>0.35</td>
<td>42</td>
<td>44</td>
<td>100 (+)</td>
<td>...</td>
</tr>
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<td></td>
<td>4.0</td>
<td>8.5</td>
<td>0.47</td>
<td>52</td>
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<td>8.0</td>
<td>9.0</td>
<td>0.89</td>
<td>85</td>
<td>69</td>
<td>77</td>
<td>...</td>
</tr>
<tr>
<td></td>
<td>9.5</td>
<td>9.2</td>
<td>1.03</td>
<td>94</td>
<td>67</td>
<td>66</td>
<td>...</td>
</tr>
<tr>
<td>New outfit with</td>
<td>2.0</td>
<td>6.2</td>
<td>0.32</td>
<td>49</td>
<td>42</td>
<td>100 (+)</td>
<td>...</td>
</tr>
<tr>
<td>forked nasal tube</td>
<td>4.0</td>
<td>8.8</td>
<td>0.45</td>
<td>51</td>
<td>50</td>
<td>97</td>
<td>...</td>
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<td></td>
<td>8.0</td>
<td>8.7</td>
<td>0.92</td>
<td>90</td>
<td>65</td>
<td>67</td>
<td>...</td>
</tr>
<tr>
<td>New outfit with</td>
<td>10.0</td>
<td>10.7</td>
<td>0.93</td>
<td>91</td>
<td>90</td>
<td>99</td>
<td>...</td>
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<tr>
<td>mask</td>
<td>9.0</td>
<td>8.9</td>
<td>1.01</td>
<td>94</td>
<td>92</td>
<td>97</td>
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</tr>
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<td></td>
<td>5.0</td>
<td>10.5</td>
<td>0.47</td>
<td>53</td>
<td>53</td>
<td>100</td>
<td>...</td>
</tr>
<tr>
<td></td>
<td>4.0</td>
<td>10.5</td>
<td>0.37</td>
<td>45</td>
<td>44</td>
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</tr>
<tr>
<td></td>
<td>2.0</td>
<td>10.5</td>
<td>0.19</td>
<td>30</td>
<td>30</td>
<td>100</td>
<td>...</td>
</tr>
</tbody>
</table>

* In some instances with the Haldane mask and with our own apparatus we have found the observed alveolar oxygen percentage to be considerably higher than the calculated. This was especially the case when the extra air inlet was not quite adequate. Under these circumstances, the accumulated oxygen is sucked into the mask more readily than the extra air, there being, therefore, a higher percentage of oxygen in the air inspired at the beginning of inspiration than at the end. Thus the percentage of oxygen in the alveolar air may be actually higher than the average percentage in the inspired air. This increased efficiency is not advantageous in practice, as it is obtained at the expense of a slight but appreciable respiratory resistance.
NOVASUROL:
A NEW DIURETIC.

BY
A. R. GILCHRIST, M.B., Ch.B. Edin.
Deputy of Botany and Silviculture, Edinburgh
University.
H. Whitridge Davies and A. Rae Gilchrist

pheres. The British Oxygen Company, Ltd., has furnished us with the following particulars. Cylinders of 100 cubic feet capacity are generally lent by the Company free of charge for one month, after which rental is payable at the rate of 6d. per cylinder per week. The present cost of new cylinders of this size is approximately £3 each. The price of oxygen in these cylinders is 35s. per 1000 cubic feet. In the small cylinders of 20 to 40 cubic feet the cost is 1d. to 1½d. per cubic foot, delivered in the local area where oxygen factories are situated. As a cubic foot contains 28.32 litres the cost of oxygen administration at any rate of flow can readily be determined.

We wish to acknowledge our indebtedness to Professor Murray Lyon for permission to make observations on the cases in his wards, and for helpful criticism in the preparation of this paper.

Our thanks are due to Mr John Flett, Technical Assistant, for analysis of some of the alveolar air samples.

REFERENCES.

NOVASUROL:
A NEW DIURETIC.

BY

A. R. GILCHRIST, M.B., Ch.B. EDIN.

(FROM THE DEPARTMENT OF THERAPEUTICS, EDINBURGH UNIVERSITY.)
NOVASUROL: A NEW DIURETIC.

Certain advanced forms of cardiac failure frequently prove refractory to all therapeutic measures, and this is notably the case when digitalis, dieting, and the common diuretics have no effect in removing the oedema. Therefore, any drug which could be relied upon to invoke a profuse diuresis, relieving the overburdened ventricle, would be assured of a permanent place in therapeutics.

Novasurol was originally introduced by the Bayer Company as an organic compound of mercury for the treatment of syphilis, its composition being sodium-oxymercuric-ortho-chlorophenol oxylacetate with dimethyl malonylurea. Later its diuretic properties were noted by Saxl and Hellig. The drug is put up in sterile ampoules and is administered in doses of 1–2 c.cm. by intramuscular or intravenous injection, each c.cm. containing 0.1 g. of the drug. As a test of its capabilities we have employed the drug in several cases of advanced cardiac failure where the response to digitalis, the diuretics in common use, and the usual therapeutic measures was unsatisfactory—in fact, where the patient's clinical state was virtually at a standstill. As a means of comparing its effects the drug has also been administered to certain other cases. Records of ventricular rate, 24 hours' volume of urine, weight, and vital capacity (V.C.) have been kept throughout treatment—the fluid intake was kept approximately constant. The dose employed was generally 1 c.cm. injected into some oedema-free area, either the buttock or back. Subcutaneous injection must be avoided, as the drug acts as an intense local irritant.

Clinical Records.

A few clinical examples of its use and effects may be recorded:—

Case 1.—Mrs. J. A., aged 43, was an in-patient from Feb. 15th to April 23rd, 1924. She was admitted in an advanced stage of failure, which responded well to digitalis and the usual measures. The diagnosis was mitral stenosis with auricular fibrillation. Quinidine restored the normal
The Use of Massive Doses of Digitalis

BY

A. RAE GILCHRIST, M.B., M.R.C.P. Ed.

(From the Department of Therapeutics, University of Edinburgh)
rhythm which persisted until she was readmitted on May 21st, 1925, with failure more advanced than before, and accompanied by a secondary anemia. Digitalis slowed the heart without benefit to her general condition, the edema increased, and the urine output fell to 900 c.c.m. Diuretin and pot. acetate were employed without effect. Novasurol was then tried with excellent results. It was necessary to employ the drug on seven occasions, and on the days following its use her urine amounted to 1800, 3300, 3000, 1800, 3300, 2400, and 3900 c.c.m. She lost 17½ lb. in weight. This was accompanied by marked clinical improvement, and she was discharged in good health on August 8th, 1925. This case is shown graphically (see figure).

CASE 2.—J. P., aged 25, suffered from mitral and aortic regurgitation with auricular fibrillation. There was much ascites present, ventricular rate 120, V.C. 55 per cent., and urinary output measured 1000 c.c.m. Digitalis produced some improvement (V.C. = 75 per cent.), but a certain amount of ascites persisted. He now received four injections of novasurol at intervals after massive doses of digitalis. His urine measured 2280, 3300, 4050, and 1200 c.c.m. The V.C. now rose to 97 per cent. Having lost 17½ lb. in weight, he was discharged on April 9th, 1925. He was readmitted with similar symptoms on the 28th, and novasurol was repeated without previous digitalisation. Urine output increased from 750 c.c.m. to 2400 and 3300 following two doses, and the heart rate fell from 120 to 66 in 24 hours. The edema and ascites disappeared. Digitalis was now employed and his condition improved steadily. On discharge his V.C. was 89.4 per cent., weight lost = 14½ lb., and heart rate = 80.

CASE 3.—A. S., aged 29, suffering from advanced failure due to mitral and aortic disease with auricular fibrillation. Digitalis and diuretin were employed with some benefit, but the edema and ascites persisted. Novasurol was now employed. The first three doses had little effect, but the fourth, given when fully digitalised, raised his urine output from 960 to 4050 c.c.m. on the following day. Steady improvement now set in, his V.C. rising from 32.5 per cent. to 65.5. He lost 5½ lb. in weight and was discharged on April 26th, 1925. He was readmitted on July 31st with similar symptoms. The same lines of treatment were carried out, and novasurol provoked diuresis of 2300, 2880, 2320, 1800, 2280, and 2760 c.c.m., whereas digitalis alone was relatively ineffective. He was discharged on Oct. 14th, having lost 41 lb. in weight, and with a V.C. of 61.4 per cent.

CASE 4.—Mrs. E. N., aged 50, was a patient from Jan. 9th, 1925, until her death on April 24th. She suffered from advanced cardiac failure, secondary to chronic bronchitis and emphysema of 10 years' duration. There was great edema extending from the feet to the back, and much ascites. Her urine averaged 600 c.c.m. for the first ten days in bed. Heart was regular (V.C. = 28.4 per cent.). Digitalis, diuretin, urea, repeated doses of calomel, theocin, and caffeine were all tried without benefit. Novasurol had little or no effect.
Case 1.—Showing urine output in litres per 24 hours (larger figures at left) and ventricular rate per minute (smaller figures at left). The + sign indicates that a portion of the 24 hours' sample of urine was lost on that day. The time during which digitalis, diuretin, and potassium acetate were administered is indicated by the horizontal lines; each injection of novasurol (1-0 c.c.m.) is represented by a vertical line. The lower figures indicate days in the ward.
Case 5.—Mrs. M. A., aged 52, gave a history of five attacks of rheumatic fever. The heart rate was 150, regular, and a diagnosis of mitral and tricuspid incompetence was made. There was ascites, and generalised oedema was present, which reached enormous proportions in the legs. Urine output average = 600–900 c.cm., and V.C. was 28 per cent. A massive dose of digitalis slowed the heart, but did not relieve her condition, and urine remained as before. Novasurol induced a diuresis of 2160 c.cm., but improvement was not maintained, and further repeated injections with and without simultaneous administration of digitalis were ineffective. Diuretin, theocin, repeated doses of calomel, Guy's pill, &c., were without avail, and she died on July 11th, 1925.

Commentary.

Of the five cases now reported two failed to respond satisfactorily to the drug. In one, Case 4, diuresis was not produced, and in the other, Case 5, although temporary improvement set in after its use, this was not maintained. Those that responded suffered from auricular fibrillation. In Case 4 the myocardial failure was secondary to long-standing pulmonary trouble, and it is unlikely that any drug could overcome the mechanical causes of the cardiac failure here present. Drugs can only alleviate cardiac failure in so far as the myocardium is able to avail itself of the help offered. In Case 5 the failure to respond to the preliminary diuresis induced by novasurol must be attributed to the fact that the heart muscle was so damaged that its activity bore no relationship to the bodily needs. In both these cases the ventricle was completely exhausted. Further experience will teach how to select those cases which will be able to benefit by the use of the drug, but it is noteworthy that in both unsuccessful cases the vital capacity was reduced to less than 30 per cent. (calculated on West's standards). Peabody's researches have shown the value of vital capacity in following the course of cardiac disease and as a guide to treatment. Both cases also suffered from intense venous engorgement, and in Case 5 the venous blood pressure (Young's method) reached 28 cm. of blood, the normal value being about 10–14 cm. by this method. In Case 1 the results were dramatic; here digitalis and diuretin were of no value, and improvement set in as soon as diuresis lessened the ventricular burden. Cases 2 and 3 also demonstrate conclusively the drug's value, and, as would be expected, the diuresis produced is greater when the patient is fully digitalised. It bears a resemblance to Guy's pill in this respect. The urine output also depends upon the amount of tissue fluids present on which the drug may act.
Novasurol, therefore, appears to be a most suitable adjuvant to digitalis therapy, and is apparently more reliable and more potent than any other diuretic at present in use. Pisani\(^5\) has recorded five cases in which the drug was effective when other remedies, such as theocin, digitalis, and strophanthin, had failed. Oerting\(^6\) had five successful cases out of a total of ten, and in Crawford and McIntosh's series\(^7\) two of eight cases were unsuccessful. Most authorities agree that owing to the presence of mercury in the drug renal disease is a contra-indication to its use. Keith, Barrier, and Whelan\(^8\) have, however, recently reported 12 cases of nephritis successfully treated with ammonium chloride and novasurol. This appears to open up an increased field of usefulness for the drug.

**Conclusions.**

1. Novasurol is a diuretic of great value in cardiac failure. It appears to be of greater potency and certainty than any of the other diuretics in common use.

2. When employed with digitalis each enhances the other's action.

3. It is suggested that cases which do not respond to the drug have a very low vital capacity, and it is unlikely that any diuretic would be helpful to such hearts.

My thanks are due to Prof. Murray Lyon for placing these cases at my disposal, and for his helpful criticism and advice in connexion with this work.

**References.**

3. The Use of Massive Doses of Digitalis.
THE USE OF MASSIVE DOSES OF DIGITALIS.

By A. RAE GILCHRIST, M.B., M.R.C.P. Ed.

(From the Department of Therapeutics, University of Edinburgh.)

Digitalis is absorbed from the bowel much more quickly than it is excreted. The concentration of the drug in the body therefore gradually and steadily rises until a level is reached at which toxic symptoms appear. It has been shown that the full therapeutic effect of digitalis is produced by an amount of the drug just short of the toxic dose, and this remains true whether repeated small doses or large single ones are employed. With the smaller doses the full benefits of the drug may not ensue for four to seven days, with massive doses the aim is to approach a similar concentration of the drug in the tissues much more rapidly. Cushny\(^1\) has aptly compared the administration of digitalis to a simple chemical titration in the laboratory. Where the strength of the reagents is known, it is safe to run in from the burette a relatively large quantity in bulk, and then complete the reaction with a few drops as the end point is reached. This is the underlying principle in the administration of digitalis by the massive dose method.

To use the method in practice, it is therefore essential to know the strength of the digitalis preparation employed and how much digitalis the patient can tolerate. As the chemical composition of the active principles of digitalis is unknown, preparations of the drug are standardised by means of pharmacological assay on cats or frogs, the result being expressed in "cat-units" or "frog-units." Tinctures of digitalis supplied by reliable firms in this country are always sufficiently standardised, but not as a rule in terms of "cat-units." The "cat-unit," on the average, has been found to correspond to 100 mgms. of the powdered leaf, 1 c.c.m. of the tincture, or 10 c.c.m. of the infusion, —i.e., a reliable tincture should have a strength of one "cat-unit" for each c.c.m.

Dosage.—Eggleston\(^2,3\) in his important work on this subject calculated the amount of the drug in "cat-units" that was required to produce maximum therapeutic effects, and found that this bore a relationship to the body-weight. In thirty-three observations the average therapeutic dose required to produce maximum
beneficial effects was found to be 0.146 c.cm. of a standard tincture per pound of body-weight. Applying these figures the dose of digitalis required to produce maximum effects can readily be calculated. High-grade tinctures on the average have a strength of 1 c.cm. to the “cat-unit,” and for convenience the dose may be estimated as $0.15 \times \text{“cat-unit” value} \times \text{pounds of body-weight} = \text{c.cm. of the tincture—e.g. patient's weight} = 140 \text{ lb.} $ $ \text{“cat-unit” value of a standard tincture} = 1 \text{ c.cm.} $ Therefore the amount of tinct. digitalis required = $0.15 \times 1 \times 140 = 21.0 \text{ c.cm.} $ A patient weighing 10 stone would therefore require a total of 21 c.cm. of a tincture of digitalis of the standard strength. When the strength of the digitalis preparation is unknown then it is wise to give only 75 per cent. of the amount calculated. Even in urgent cases of heart failure it is most important that none of the digitalis preparations should have been employed within fourteen days previous to the giving of the full dose as calculated by Eggleston's method. In all cases the dose should be measured accurately, and it is preferable that the tincture should only be diluted with water immediately before its administration. When it is desired to employ the massive dose method, it has been recommended that the total amount calculated from the formula be divided into three doses and administered as follows: $\frac{1}{3}$ to $\frac{1}{3}$ of the total, then $\frac{1}{3}$ to $\frac{1}{3}$ of the total, followed by $\frac{1}{3}$ to $\frac{1}{3}$ of the total and the remainder in a few small doses. The doses are given at 4 to 6-hour intervals. Gratifying results from this line of treatment have been reported by Kay and by White and Morris. Robinson has administered the full calculated amount in a single dose to 100 cases of heart disease and observed excellent results.

The Eggleston method has been modified slightly to make it more convenient in general use, particularly in those instances where the “cat-unit” strength is not definitely known, and where the patient's weight cannot be accurately determined. Fraser, from his experience of the method, recommends the administration of $\frac{1}{3}$ drachms, 1 drachm, and $\frac{1}{3}$ drachm of a high-grade tincture at six-hour intervals for patients of 8 stone and over. This is a safe and reliable method for rapidly bringing the heart under the influence of the drug. Similar considerations led Pardee to recommend that when a tincture of unknown strength must be employed, it is safe to give the patient 1 minim for each pound of body-weight when calculating a single massive dose. As such an amount is less than that calculated from Eggleston's figures a wide margin is allowed.
The Use of Massive Doses of Digitalis

for in the strength of the tincture. In private practice where the use of precise figures for the calculation of the full dose is not practicable, good results may be obtained with safety by administering 15 minims of the tincture for each stone of body-weight as a single massive dose, and following cautiously with 20 minims at six-hour intervals until full therapeutic effects are produced, or until the earliest signs of intoxication appear. This method is compared with Eggleston's in the accompanying table.

CALCULATED AMOUNT OF TINCT. DIGITALIS.

<table>
<thead>
<tr>
<th>Normal Weight in Stones</th>
<th>I. By Eggleston's Method in c.cm.</th>
<th>II. By Pardee's Method (modified) in Drachms.</th>
</tr>
</thead>
<tbody>
<tr>
<td>8</td>
<td>16.8</td>
<td>2.0</td>
</tr>
<tr>
<td>9</td>
<td>18.9</td>
<td>2.25</td>
</tr>
<tr>
<td>10</td>
<td>21.0</td>
<td>2.5</td>
</tr>
<tr>
<td>11</td>
<td>23.1</td>
<td>2.75</td>
</tr>
<tr>
<td>12</td>
<td>25.2</td>
<td>3.0</td>
</tr>
<tr>
<td>13</td>
<td>27.3</td>
<td>3.25</td>
</tr>
<tr>
<td>14</td>
<td>29.4</td>
<td>3.5</td>
</tr>
<tr>
<td>15</td>
<td>31.5</td>
<td>3.75</td>
</tr>
<tr>
<td>16</td>
<td>33.6</td>
<td>4.0</td>
</tr>
</tbody>
</table>

This table shows the dose of tinct. digitalis calculated by two methods on the body-weight. In estimating the dose it is well to employ the patient's assumed normal weight, disregarding any excess due to oedema or ascites, etc. For a given weight Eggleston's method yields the larger dose. Pardee's method is simpler, the dose being calculated on the basis of 15 minims per stone. Should maximum therapeutic effects not be produced by this dose within twenty-four hours, then repeated doses (20 minims) at six-hour intervals may be commenced and cautiously continued until the desired effects or earliest toxic symptoms appear.

To use the massive dose method to the best advantage, the administration of the drug should be commenced when the symptoms of heart failure are most urgent. The best results are obtained in cases of auricular fibrillation accompanied by marked congestive failure and high ventricular rates. When maximum beneficial effects from the large doses have been obtained then small doses of 10 to 20 minims thrice daily can be recommenced in order to hold the ventricle at the most suitable rate. We have employed Eggleston's method not only in urgent cases but have also administered massive doses at fortnightly intervals in order to study the response to digitalis in different types and stages of heart failure, and the results in cardiac failure accompanied by auricular fibrillation are now reported.
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**Technique Employed.**—Before the digitalis was given the patient was allowed several days' complete rest in bed in order to eliminate the effects of the natural slowing in cardiac rate, which so frequently occurs, even in acute cases of cardiac failure, under good nursing, complete rest, and hospital regime. In one or two cases, the urgency of the symptoms would not permit of this delay. The others have all had four to six days' complete rest in bed without drug treatment, save routine measures, before digitalis therapy was commenced, and even up to ten or fourteen days if any of the digitalis preparations had been recently prescribed before the patient's admission to hospital. Daily records of ventricular rate and pulse deficit for the same minute have been taken in all cases. Urinary excretion was measured daily, and the patient's fluid intake kept approximately constant over the time that the digitalis was employed. So far as possible conditions have been kept constant, so that the effects produced by massive doses might be compared under standard conditions, but as a general rule, with improvement in the patient's condition during his stay in hospital, this was liable to some slight alteration; and the effects produced by massive doses were naturally more dramatic in the earlier stages of treatment than later, when the urgent signs of failure had to a large extent subsided. In each case the full amount of powdered leaves calculated from Eggleston's formula was administered in three doses at four-hour intervals, and in practically all cases the method was employed on more than one occasion.

**The Response to Massive Doses.**—We have employed Eggleston's method of rapid digitalisation on over fifty occasions in cases of auricular fibrillation. As a general rule slowing of ventricular rate occurs within six hours, and maximum effects are reached in fifteen to twenty-four hours and often persist for several days. It is well known that in this condition many of the heart beats are so feeble that they cannot be felt at the wrist, and for this reason it should be pointed out that in the early stages of digitalis action, the pulse rate is not a reliable guide, for it may appear to accelerate owing to the increased force of the ventricular contractions allowing more beats to reach the wrist. In auricular fibrillation alterations in heart rate can only be observed with accuracy by counting with the stethoscope. As the heart becomes steadier in action and each beat stronger, so the general circulation improves. Diuresis may set in as the ventricular rate slows, and the
The Use of Massive Doses of Digitalis
dyspnoea often decreases in a remarkable manner. As a result, the patient becomes more comfortable, and is often rewarded by a profound and restful sleep. In urgent cases of failure with this disorder of rhythm the results are generally most gratifying, and in some cases the time gained by this therapeutic procedure has been life-saving. Such an example of its use may be recorded:

CASE—A. S., aged 30, suffering from rheumatic mitral stenosis and aortic regurgitation accompanied by auricular fibrillation. He was admitted to hospital on 31st July 1925 in a state of advanced cardiac failure. There was generalised oedema of the trunk, legs, arms, face and chest wall. Jaundice was present, and the extremities and face were markedly cyanosed. The abdomen was enormously distended with ascitic fluid, and the lower edge of the liver reached the level of the umbilicus. Both lungs were congested, and the urine amounted to only 300 c.c. in the twenty-four hours. Heart rate = 150, radial pulse = 78; respirations = 32 per minute. On the following day his condition became worse, respirations more laboured, food was refused and he became semi-conscious, a mild degree of acidosis developing. The heart rate was 178, and respirations = 48. He was incontinent, extremities cold, and in the arms and legs the oedema reached enormous proportions. He was given a total of 2 grams of digitalis leaves (= 5 drachms of digitalis tinct.) divided into 3 doses in the course of eight hours. His heart rate fell from 178 to 82 in less than twenty hours; his respirations fell to 24; he regained consciousness, and the following day was able to sit up in bed, and take an interest in the work of the ward. His urine output increased, and the ascites diminished, and steady clinical improvement set in.

In this case the full digitalisation produced in the course of a few hours, with the consequent improvement in the general circulation rate, was the prime factor in tiding the patient over a period when his life was despaired of.

In practically all our cases the time taken to produce the maximum amount of slowing of the heart was less than twenty-four hours from giving the first dose. Slowing might be delayed in cases of acute heart failure with evidence of marked venous congestion. Congestion of the portal system with consequent slowing of the circulation rate must undoubtedly retard absorption of the drug, and this may be a factor in those cases, where, though marked slowing was induced, the maximum effect was not reached until thirty-six or forty-eight hours after the administration of the drug had been commenced. Occasionally mild toxic symptoms such as
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nausea, anorexia, or vomiting have been observed, and these might be responsible for obscuring the full effects on the heart rate while they lasted.

The duration of the effect of massive doses on cardiac rate has been studied in these cases by observing for how many days the ventricle remained within ten beats of the lowest recorded rate. This has been found to vary between two and ten days, and depends probably on many factors. In fibrillation, the rate is largely controlled by the degree of block present in the bundle of His. The number of impulses emitted by the auricle remains fairly constant from case to case, and the acceleration of the ventricle results from a greater facilitation of the passage of impulses along the bundle. The heart embarrassed by auricular fibrillation is more susceptible to some intercurrent condition—e.g. exertion, sepsis, excitation, etc., than the normal heart, and, therefore, observations on the duration of the effect produced in cardiac slowing are open to considerable error. Different cases show a varying response in this respect.

The diuretic effect of digitalis is only seen in the presence of edema of circulatory origin, and with massive doses of digitalis the urine output not only increases as the ventricle slows in rate, but frequently continues in increased volume for some days after the dose has been given. One massive dose may be insufficient in itself to remove all the edema, this depending on the degree of failure, the ability of the myocardium to respond to the drug, and also on the state of the kidneys. In certain advanced types of failure accompanied by auricular fibrillation, it is common knowledge that even as the heart slows under digitalis, the edema and anasarca may increase in amount in the absence of the desired diuresis. Such an event is less common in those cases of fibrillation of rheumatic origin than in the arteriosclerotic group with renal complications. The amount and duration of the diuresis induced by massive doses is therefore of some value in forming a prognosis.

Toxic Effects of Massive Doses.—The toxic effects of massive doses are similar to those which result from the continued administration of small doses. Withering\textsuperscript{11} in his original account of the foxglove and its medical use said: "Let the medicine (digitalis) be continued until it either acts on the kidneys, the stomach, the pulse, or the bowels; let it be stopped on the first appearance of any of these effects, and I
The Use of Massive Doses of Digitalis

will maintain that the patient will not suffer from its exhibition." This rule holds good for the use of massive doses, and should signs of intoxication make their appearance before the total amount has been administered then the following dose must be withheld.

Only a little more digitalis than will produce maximum therapeutic effects is tolerated by the tissues, and symptoms of intoxication ensue when this narrow limit has been encroached upon. Though a mild degree of digitalis intoxication has been fairly common after these large doses, toxic effects of any importance have been surprisingly rare and of short duration.
The symptoms of intoxication most commonly complained of have been slight frontal headache, often described as a heavy sensation behind the eyes, and slight anorexia, or nausea as a rule only of a few hours' duration. Other cases have suffered from vomiting of one to two days' duration, but never sufficiently severe to cause anxiety. Many cases have been drowsy for twenty-four hours or more after the whole dose had been administered. It is doubtful if this can be described as a toxic symptom, because sleep is often of great relief to a cardiac patient. This symptom occurred regularly in several patients who complained of slight nausea and malaise after repeated massive doses, and who had been sleeping well at night previous to the drug's administration. None of our cases have suffered from diarrhoea, and the rarer toxic manifestations such as delirium or amnesia have never been observed.

In observing cases during the administration of massive doses it is important to distinguish between the toxic symptoms of digitalis and similar symptoms arising from other causes. At least six hours must elapse before a single dose of digitalis can be absorbed from the gastro-intestinal tract, and nausea or vomiting occurring within such a period from the time of taking the drug should not be attributed to digitalis intoxication, but rather to local gastric causes. Hatcher and Weiss\(^{10}\) have shown that emesis only occurs when the nerve supply to the heart is intact, the vomiting centre being stimulated by impulses passing up from the heart by way of the sympathetic and vagus nerves. In the presence of any gastric irritability, it may be useful to combine the first dose with tincture of opium, but this must be small in amount in order not to obscure any true toxic effects should they ensue. Should nausea or vomiting commence before the whole of the calculated amount of digitalis has been administered, then it is wise to omit further doses until these
The Use of Massive Doses of Digitalis

and concerning this fact, it is undoubtedly surprising that such large doses of the drug have been tolerated without greater disturbance. This may be taken as evidence of the safety of the method, but nevertheless the patient must be kept under fairly frequent observation while the large doses are being administered.

Conclusions.—(1) As the ventricle is brought under control rapidly, the method of massive dosage has its greatest value in cases of auricular fibrillation, which at all times is that disorder of rhythm giving the best response to digitalis medication. In cases of fibrillation secondary to rheumatic infection, acutely ill, with marked venous congestion and high ventricular rates, the results are often dramatic. Such cases are not likely to be mistaken for any other condition, and it is in them that often the practitioner will find large doses of the greatest value.

(2) In cases of fibrillation secondary to chronic myocardial degeneration and accompanied by advanced arteriosclerotic and renal changes, the method is not always of such value as in the former group, but may be used if the symptoms demand it.

(3) In urgent cases the method is less dangerous than the intravenous administration of strophanthin.

(4) The response to massive doses is of some value in forming a prognosis.

(5) From the practitioner’s point of view Fraser’s method or Pardee’s may be employed. It is easy to calculate the dose on the basis of 15 minims of the tincture for each stone of body-weight, and give 20 minims six hourly thereafter until maximum therapeutic effects are obtained.

(6) Toxic effects are rare and can be largely avoided by keeping the patient under fairly frequent observation.

Professor Murray Lyon has given me every facility to study the cases in his wards, and for this, and his constant help and advice, I have pleasure in expressing my thanks.

2 Eggleston, Arch. of Int. Med., 1915, xvi., 1.
5 White and Morris, Arch. of Int. Medicine, 1918, xxii., 740.
7 Fraser, The Lancet, 1922, ii., 703.
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symptoms have passed off. This is a safe and reliable procedure if the total amount is divided into three doses at intervals of six hours.

The toxic effects of digitalis on the heart are well known since Mackenzie pointed out that it may give rise to heart-block, various irregularities of impulse formation and even pulsus alternans. In these cases of fibrillation secondary to rheumatic valvular disease, we have observed no toxic effects on the heart, save occasionally the occurrence of extra-systoles which might be attributed to the drug. In other cases of tachycardia with normal rhythm, partial heart-block and a marked sinus arrhythmia have been induced on two or three occasions. It is known that digitalis tends to perpetuate auricular fibrillation, and its beneficial action in this condition, results, not from restoring the normal rhythm, but by slowing and strengthening the ventricular contractions. In four cases we have seen a regular normal rhythm followed by auricular fibrillation after massive doses of digitalis without any detrimental effects to the patient's general condition. Cushny states\(^9\) that perhaps in all the cases where digitalis is said to have induced fibrillation the previously regular ventricular response was accompanied by auricular flutter. This was not so in our cases. In two cases the normal rhythm returned after a day or two, in another fibrillation persisted until death, some months later, and in the other case quinidine induced a return to normal rhythm on two occasions after fibrillation had been produced by massive doses of digitalis. Two of these cases may possibly have suffered from attacks of paroxysmal auricular fibrillation previous to the use of digitalis. On each occasion, however, on which the digitalis was employed the normal rhythm gave place to fibrillation when the digitalis had reached its maximum concentration in the tissues.

In the second group of cases of auricular fibrillation accompanied by advanced degeneration of the myocardium secondary to arterial or renal disease, as distinct from those cases of purely rheumatic origin, toxic effects have been fairly frequent. Pulsus bigeminus lasting for a few days has been noted on one or two occasions, and in one case with advanced renal and arterial disease, the administration of massive doses was definitely related to the production of paroxysmal tachycardia of ventricular origin. It is known that, where there are already extensive lesions of the myocardium, digitalis will more readily produce disorders of rhythm,
4. The Relation of Digitalis Administration to Paroxysmal Ventricular Tachycardia in Man.

The relation of Digitalis administration to paroxysmal ventricular tachycardia is of some interest. Though this type of paroxysmal tachycardia is relatively rare, it is of interest to note that Digitalis has been used successfully in its treatment. In a recent case, a patient exhibited paroxysmal tachycardia following the use of Digitalis and strychnine, but it was not possible to obtain clear tracings to confirm this diagnosis. The use of Digitalis in cases of ventricular arrhythmia has been recognized as a cause of further distress in man. Danielsson (3) reported three cases of paroxysmal tachycardia following the use of Digitalis and strychnine, but it was not possible to obtain clear tracings to confirm the diagnosis. The use of Digitalis in cases of ventricular arrhythmia has been recognized as a cause of further distress in man.
Paroxysmal ventricular tachycardia is regarded as one of the rarest of the cardiac arrhythmias, but with the increasing use of the electrocardiograph, cases are now being more frequently recognised and the significance of the condition better understood. It is not proposed to review fully the literature on this subject as this has been done recently by Wolferth and McMillan (1). In reporting their four cases, twenty-two others are referred to by these authors.

The relation of digitalis to paroxysmal ventricular tachycardia is of some interest. Though this type of rhythm is known to occur in animals after the use of toxic doses of the digitalis preparations, it is only recently that the drug has been recognised as a cause of the disorder in man. Daniélopolu (2) reported three cases of paroxysmal tachycardia following the use of digitalis and strophanthin, but it is not possible from his tracings to credit the tachycardia with a ventricular origin. Eggleston and Wyckoff (3) in their work on digitalis therapy, mention one case where recovery /
recovery occurred, and Schwensen (4) has also noted the relationship. Felberbaum (5), reporting a similar case with a regular tachycardia in whom alternate complexes varies in direction, suggested digitalis as the provoking cause. Wolferth and McMillan (1) noted that in one of their cases ventricular tachycardia followed the use of digitalis but the evidence did not suggest that the drug was the precipitating cause of the attack. Reid (6) has recently described five cases in whom the amount of digitalis administered before the onset of the paroxysms was well in excess of that indicated by the Eggleston method. In one case in whom the ectopic tachycardia was associated with an alternating mechanism in the form of the $Q - R - S - T$ deflection, the change to ventricular fibrillation was recorded with the electrocardiograph as death ensued. These five cases suffered from an advanced degree of congestive failure associated with auricular fibrillation. Luten, (7) in his studies on the toxic rhythms of digitalis in man, noted two cases with idioventricular rhythm and abnormal complexes. In one of these, and three others (8) an alternating mechanism was present during the paroxysms. He suggests that an advanced degree of digitalis intoxication may result in a paroxysmal tachycardia which originates at, or near, the main stem of the bundle, alternate impulses being partially blocked by one branch of the bundle and transmitted by the other, and so on. This mechanism would account for the rhythmic alteration in the direction of the $Q - R - S - T$ deflection. He finds that the toxic effects of digitalis on the human heart resemble closely those observed on the heart of the cat.

Clinical /
3.

Clinical Cases.

Case I. Mrs. M.A. aged 52, was a patient from 28.4.25 until her death on 14.7.25. She gave a history of five attacks of rheumatic fever, the first at age 20, but admitted no cardiac symptoms until two months previous to hospital treatment, when an irritating cough began to bother her. This was followed rapidly by dyspnoea on exertion, and later by orthopnoea and a copious white frothy sputum. Three weeks previous to admission, oedema of the ankles appeared, and in the course of a day or two spread up to the hips and back. Since then both hands had swollen at times, and the abdomen had become more and more distended. Examination revealed a "water-logged" patient, pale and cyanosed. There was generalised oedema, which reached enormous proportions in the legs, and a tremendous amount of ascites, with enlargement of the liver. Heart was regular in rhythm, 150 per minute, auricular flutter present, with marked venous engorgement of the superficial veins. The transverse diameter of the heart in the 4th space was 19 cm., tic-tac gallop rhythm present, with mitral and tricuspid incompetence. There was no hydrothorax present, but marked congestion of both pulmonary bases. The urine contained a trace of albumen. Blood Wassermann reaction was negative. The vital capacity was 800 c.c. - less than 28 per cent. of the normal. (West's (9) standards). The venous blood pressure was 28 cm. of blood. (Young's (6) method). A massive dose of digitalis reduced the heart rate to 75 (4 to 1 flutter) without improvement in the patient's general condition. A few days later the rhythm changed to auricular fibrillation, and finally normal rhythm returned fourteen days after the single massive dose of digitalis had been given. Novasurol induced a slight diuresis, but improvement was not maintained. Later small doses of Guy's pill twice daily were ineffective during a week's trial. This was followed by 0.4 grm. pulv. digitalis daily. Three days after commencing this preparation extra-systoles were noted and a single short run of pulses bigeminus. Her condition seemed better and the digitalis was continued for three more days when paroxysmal ventricular tachycardia appeared, the attack lasting for nearly 36 hours - with a ventricular rate of 170. (Fig. 1). Digitalis was stopped and electrocardiograms taken on the cessation of the paroxysm showed normal rhythm with numerous extra-systoles frequently in groups and followed by delayed AV conduction. Her condition was now definitely worse, slight jaundice present, and as all the usual diuretics were without avail, venesection, and Southey's tubes to the legs, were employed. Extra-systoles became less and less frequent as normal rhythm persisted. Pulsus bigeminus returned for a day or two. Ten days before her death she had a series of convulsions, each of which lasted from one to five minutes, and was characterised by rapid clonic movements of the extremities, deviation of the head and eyes to the left, and in the intervals much mental confusion and transient attacks of asphasia. The heart rate during the fits was 140 or more, and regular, but the type of rhythm present could not be ascertained. The legs became septic, and she died peacefully on 14.7.25. A post mortem examination was not obtained.
from this case are shown in fig. 1. The diagnosis of ventricular tachycardia depends upon the evidence of independent and rhythmic auricular activity during the paroxysm, and upon the close resemblance between the ventricular complexes with extra-systoles recorded before and after the paroxysm. That digitalis was the provoking cause seems evident from the fact that coupled rhythm preceded and succeeded the paroxysm, and that the premature beats became progressively less numerous after the drug had been discontinued.

Case 2. R.M., male, aged 64, was a patient from 4.12.24 until his death on 27.2.25. There was no history of rheumatic fever but he had always been a heavy drinker, consuming whisky and beer daily for years. His occupation required much muscular activity, and for the last two years he had found it increasingly difficult. Giddiness, breathlessness on exertion, nocturnal frequency of micturition, and precordial pain, had become increasingly severe during the past two years, and for a few weeks previous to admission to hospital oedema of the ankles, and ascites, had been present. Examination revealed the presence of auricular fibrillation with advanced congestive failure. The apex beat was in the sixth space 16 cm. to the left. There was marked arterio-sclerosis, with albuminuria, casts and urinary output of 300 - 1000 c.cm. per twenty-four hours. Blood urea was 36 mgm. per cent.; phenolphthalein excretion was 11 per cent in two hours. Blood Wassermann reaction negative. Vital capacity 1600 c.cs. - approximately 37 per cent of the normal. The patient was treated with various diuretics, with digitalis, and the usual dietetic measures, without improvement. In all, he received four courses of digitalis therapy as shown in the accompanying diagram. The first consisted of 0.4 grm. pulv. digitalis daily for five days. Two days later the heart rate had fallen to 62, with no improvement in his condition. The drug was then stopped. Sixteen days later he received a massive dose of pulv digitalis (1.4 grm.) and this was followed two days later by a short paroxysm of tachycardia, lasting half an hour. A further massive dose (1.4 grm.) was given sixteen days after the previous one, and this was followed by two paroxysms of tachycardia, with a ventricular rate of approximately 150. Electro-cardiogram of the second attack is shown in fig. 2. It lasted for one hour and a half. Digitalis was discontinued for a fortnight, and as its repetition in small daily doses again invoked many brief paroxysms, its further use was therefore precluded. He died later, in advanced cardiac failure. A post mortem examination was not obtained.

Electrocardiograms from this case are shown in fig. 2. In two separate attacks electrocardiograms were secured.
In the others, cardiographic proof of their nature could not be obtained. The diagnosis of ventricular tachycardia is based on the abnormal type of ventricular complex present, (resembling extra-systoles) and the continuation of auricular fibrillation throughout the paroxysm. The paroxysms bore a definite relation to the administration of digitalis.

**Discussion.**

Case I received a massive dose calculated from Eggleston's formula of 2.8 grm. pulv. digitalis of standard potency which was followed by slowing in ventricular rate and slight vomiting and nausea without evidence of any toxic effect on the heart. Seventeen days later a course of digitalis therapy was recommenced and during this time (thirteen days) the patient received 3.4 grm. in all. Assuming a daily elimination and destruction of 0.15 grm. the amount given was therefore not in excess of that calculated by the Eggleston method. Paroxysmal ventricular tachycardia resulted, being preceded by coupled rhythm and succeeded by profuse extra-systoles and coupled rhythm, and this without general symptoms of digitalis intoxication - no nausea, anorexia nor vomiting. Neither the massive dose nor the course of digitalis therapy produced improvement in the patient's state, and her progress was steadily in a downward direction. The difference in the response, on the two occasions on which digitalis was exhibited in this case, might be attributed to the fact that on the second occasion the myocardium was in a more exhausted condition and more susceptible to the drug. All the cases in whom this disorder of rhythm has been attributed to digitalis, suffered from advanced congestive failure. An alternative explanation may
may be that with the advancing failure previous to the onset of the paroxysm, the active principles of the drug were less efficiently eliminated or destroyed by the tissues.

Absorption of the drug must undoubtedly have been less rapid, and this may help to explain why the premature beats of all types persisted for upwards of ten to fourteen days after the occurrence of the paroxysm and the discontinuation of the drug. A fortnight elapsed before the full sino-auricular rhythm became firmly re-established and, during this time, first the coupled rhythm, and later the irregular extra-systoles, gradually disappeared. A somewhat similar course of events was observed by Danielopolu (2) and it is probable that more protracted absorption, defective excretion and a higher degree of myocardial susceptibility towards the drug, all played a part. In this case digitalis first reduced a 2 to 1 flutter to 4 to 1, subsequently induced fibrillation, and later normal rhythm became established. A further course of digitalis was responsible for the production of paroxysmal tachycardia.

In case 2, the subject of advanced cardio-renal and arterial disease, the relation of the paroxysms to the digitalis dosage is demonstrated in the accompanying graph. In this case the paroxysms were of short duration, and though seven in all were recorded, it was only possible to obtain electrocardiographic evidence of their nature on two separate occasions - the third and the seventh in the diagram. This patient suffered from auricular fibrillation, and the amount of digitalis administered was 0.1 grm. less than that calculated by the Eggleston method. The patient's normal weight was 140 lbs., the oedema and ascites being neglected in /
in calculating the dose. No general toxic symptoms resulted, and save for the paroxysms, there was no other evidence of toxic effects on the heart muscle. With successive doses the paroxysms occurred earlier, until, during the final course, the first attack was noted after 1.0 grm. had been given. This lends support to the view that those cases become more susceptible to the drug in whom myocardial degeneration is far advanced, and in whom the degree of heart failure is steadily advancing. Apparently the underlying cause of this response to digitalis is more the state of the heart muscle than the size of the dose. In such subjects the use of massive dosage of digitalis is not without danger.

Cushny, (11) in an attempt to reconcile experimental and clinical results in the use of digitalis, has put forward the view, that in clinical auricular fibrillation the characteristic reaction to digitalis depends on the state of nutrition of the heart, as well as on the presence of the fibrillation, mal-nutrition and a high ventricular rate favouring a good response to digitalis. Nutrition must, for the present, be regarded as a relative term, for a time must come when, with advancing failure and increasing mal-nutrition, the ventricle will be unable to avail itself of the proffered help. Nutrition of the heart-muscle is an important factor in determining the heart's response.

Concerning the production of paroxysmal ventricular tachycardia by digitalis, it is of interest to note that in cases of myocardial failure with normal rhythm, digitalis may induce auricular fibrillation. This has been observed in man /
man by Mackenzie (12), Daniélopolu (13) and others. It has also been noted by the writer in four cases after full massive dosage with digitalis (14), and Resnik (15) has recently investigated this subject in seven patients showing a high degree of myocardial failure, who developed transient auricular fibrillation after digitalis therapy. He concludes that the probable predisposing factor is myocardial failure, and that digitalis acts mainly on the muscle and possibly also through the vagus in inducing this change in rhythm. May it not be that some similar mechanism underlies the production of transient paroxysmal ventricular tachycardia after the use of digitalis? Lewis's views that auricular fibrillation is a manifestation of circus movement in the auricle are now widely accepted, and the suggestion has been put forward that a similar mechanism is responsible for ectopic tachycardia in the ventricle. Circus movement, as applied to the auricle, and ventricular tachycardia, have certain features in common, (Lewis (16)), and it seems probable that, given a certain critical state of the heart muscle, e.g. profound mal-nutrition, either of these disorders may be provoked by digitalis. The manner in which digitalis induces ventricular tachycardia is not fully understood, but Robinson and Hermann (17) observed ventricular paroxysms following coronary obstruction in man, and there is evidence to suggest that large doses of digitalis may constrict the coronary arteries at least under experimental conditions. (18). In the present state of our knowledge, any discussion on the mechanism of the action of digitalis on the ventricular musculature, embarrassed by such a complex process as advancing failure, must needs be purely speculative. The drug increases rhythmicity (10), produces extra-systoles, depressed intra-ventricular conduction, and it /
it is conceivable that in the presence of a certain critical state of the heart muscle, the refractory period may shorten. Such a combination would favour the establishment of circus movement. Leaving aside theoretical considerations, the important point in the production of abnormal rhythms by digitalis appears to be the state of nutrition of the heart muscle.

In the presence of a demonstrable cardiac lesion with advancing failure and under treatment with digitalis, the occurrence of this form of tachycardia is of the most serious significance. It indicates that the ventricle is incapable of responding to the drug in a satisfactory manner and, apart from the danger of ventricular fibrillation, this disorder places an additional burden on the heart, and gradually embarrasses all the bodily functions. Such cases call for special care in the use of digitalis. Unless accurate observations are made by closely watching the heart rate, attacks may pass undetected, as in these subjects they are often unassociated with suggestive symptoms and are accompanied by a large pulse deficit. The symptoms which this disorder of rhythm may produce in the absence of an advanced cardiac lesion are well known, and are apparently proportionate to the duration of the attack. Yet in case I, in whom the paroxysm persisted for about thirty-six hours, symptoms were obscured by the advanced congestive failure already present. Congestive failure increasing in amount during the course of a few hours points to the presence of a change in the type of rhythm and requires careful investigation. As a general rule each paroxysm must run its own course. In these two cases many opportunities occurred for the trial of those procedures which on occasions may abolish the
the attacks. Vagus and bilateral ocular pressure, and deep breathing &c. were all ineffective in each case. Quinidine has controlled the attacks in several of the reported cases (Scott (19)) but in the presence of advanced myocardial disease the use of the drug is not warranted. It is in such instances that this drug may itself produce ventricular tachycardia. The drug was therefore not employed in the two cases under discussion.

Summary and Conclusions.

It is only within the last few years that digitalis has been recognised as a cause of this rare disorder of the cardiac mechanism. To the 12 cases collected from the literature, two are added in whom it is concluded that this drug was the precipitating cause of the attacks.

These two patients were the subjects of steadily advancing congestive failure, and the dose of digitalis did not exceed that calculated on the body-weight method of Eggleston.

It is concluded that this disorder of rhythm depends more upon the state of cardiac nutrition than on the degree of concentration of the drug in the tissues.

It is suggested that a mechanism, similar to that which underlies the production of auricular fibrillation by digitalis in cases of heart failure with normal rhythm, may also be present in these cases where the drug has provoked ventricular tachycardia.

In the presence of advanced cardiac failure, this arrhythmia may produce no characteristic symptoms. Emphasis is /
is placed on closely watching the heart in all severe cases of myocardial failure under treatment with digitalis. Clinically this is the only reliable means of recognising the presence of tachycardia.

Apart from the danger of ventricular fibrillation, this disorder places an additional burden upon the heart and tends to shorten life. Accordingly digitalis must be used with care in such cases.

The disorder is easier to avoid than to treat.

References. /
References

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8. idem - ibid p. 87.

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Fig. 1. (Case 1).

Upper record, (lead 2, 2 cm. = 1 millivolt) taken on first day of paroxysm, shows the abnormal type of complex with dissociated auricular activity. The ventricular rate is 170 and the auricular 73 per minute.

Twenty-four hours later - two middle records (leads 1 and 3) - the paroxysm still continued. The P waves are well marked in lead 1. Lead 3 shows a right-sided contraction replacing the eleventh beat. The ventricular and auricular rates are now 170 and 76 respectively per minute.

The lowest record (lead 2) taken on the day after the cessation of the paroxysm shows the return of normal rhythm with numerous extra-systoles, ventricular escape, and defective A-V conduction (.22 second). The ventricular extra-systole in this record resembles closely the ventricular complex during the paroxysm in the same lead.

* Time-marker, 28.57 vibrations equals 1.0 second. 1 cm. equals 1 millivolt in all records unless otherwise stated.
Fig. 2 (Case 2).

The upper two records (leads 1 and 3) show auricular fibrillation present throughout the period in which the patient was under observation.

Lower record (lead 2) was taken during a paroxysm of ventricular tachycardia. Irregular waves due to persistence of the auricular fibrillation can be seen between the ventricular complexes. The ventricular rate is 158, and the complexes vary in form from beat to beat.
Diagram
Diagram to show the relation of the paroxysms of ventricular tachycardia to the digitalis dosage in Case 2. The ventricular rate charted for each day is that recorded by counting at the apex. Each massive dose consisted of 1.4 grm. of pulv. digitalis. This was calculated according to Eggleston's formula from the assumed normal weight, disregarding the excess due to ascites and oedema. During the final course the patient received 0.4 grm. daily.