The activity of smaller doses of paludrine and mepacrine is now being investigated. There seems to be little to choose between single doses of paludrine and mepacrine in the treatment of the acute attack of relapsing or delayed primary benign tertian malaria, apart from the slight abdominal discomfort sometimes produced by the latter. The advantage of paludrine, however, lies in its being a colourless drug, and therefore much more satisfactory to prescribe over a long period.

It must be remembered, too, that the activity of paludrine against the exo-erythrocytic form of *P. gallinaceum* is not shared by mepacrine. The recent experiments of Fairley and his co-workers in Australia suggest that under suitable conditions paludrine may act on the as yet unidentified exo-erythrocytic forms of the human *P. vivax* parasites. It is possible that dosage with paludrine may therefore materially affect the relapse rate of chronic B.T. malaria, upon which mepacrine has little effect, if the drug is given, as described, in weekly single doses over a prolonged period.

Our results in the treatment of benign tertian malaria will possibly be exposed to the hoary criticism that the cases we have dealt with would have cured themselves without the administration of the drug. Such spontaneous recovery does occasionally occur, but this argument (which, of course, applies to all antimalarial research) practically amounts to declaring that all cases of benign tertian malaria admitted to our wards spontaneously subside after the second or third rigor. We have tried to counter it by observing all our cases before treatment until they have had at least two rigors (with unchanged or rising parasitaemia). In some cases we have allowed the patient to have five or more rigors, after which clinical cure has been obtained immediately following the administration of a single dose of paludrine. (The temperature chart of such a case is here reproduced.)

Summary

Paludrine is a colourless slightly bitter drug belonging to a class of chemical compound not previously known to have antimalarial activity. Unlike most other antimalarial drugs, it has been found to have an action on the exo-erythrocytic forms of the parasites in *P. gallinaceum* avian malaria.

It has been used successfully in the treatment of benign tertian malaria (both in relapses and in delayed primary attacks) and in acute attacks of malignant tertian malaria (both primary cases and relapses).

It has a very wide therapeutic range of activity. Doses of 10 to 750 mg. and of 50 to 600 mg. twice daily for 14 days have been used successfully in the treatment of benign and malignant tertian malaria respectively. No serious toxic side-effects have been observed with such dosages, although occasional nausea and vomiting may occur at dosages of 500 mg. or more twice daily.

The administration of single doses of 50, 100, 200, 300, and 400 mg. will produce clinical cure of relapsing and delayed primary cases of benign tertian malaria. Similar effects have been obtained with single doses of 400 mg. mepacrine.

Twice-daily dosage regimes for 14 days have no greater effect on the relapse rate of benign tertian malaria than full courses of mepacrine. The administration of one dose of 100 mg. weekly after treatment of the acute attack with a single dose of 50 to 400 mg. has so far been found to keep the patient free from relapses. The effect of this therapy over a period of six months is being investigated.

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King Edward's Hospital Fund for London has issued a revised edition of its out-patient time-table for London hospitals. All doctors in the Metropolitan Police District are receiving copies, and a considerable number are being sent to infant welfare and other health societies. This time-table helps patients and their doctors to prevent the waste of time which sometimes results from attending hospitals at the wrong hour, or even on the wrong day. A limited number of copies are obtainable free of charge from George Barber and Sons, Ltd., 23, Furnival Street, E.C.4.

EXTRARENAL URAEMIA

BY

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The appearance of renal failure in the course of organic renal disease does not seem to be either extraordinary or strange. This does not apply to those rather frequent cases of renal failure which are met with in diseases not primarily involving the kidneys, and in patients who apparently had previously never suffered from any kidney trouble. The most varied pathological conditions may give rise to this kind of renal failure. The following may be mentioned first: any disease accompanied by considerable loss of water and/or salts (vomiting and/or diarrhoea); major operations of any kind; burns; crushing and other grave injuries. Renal failure may also be observed in severe liver affections, particularly when complicated by jaundice (hepato-renal syndrome); in myocardial infarction; and in general infections of various kinds.

All these cases of renal failure are of an acute character, and are cured within a few days, or end fatally, with oliguria, anuria, and, finally, uraemic coma as their most prominent symptoms. The question arises whether these cases of *extra*-renal or, according to Fishberg (1939), *pre*renal uraemia have a common basis, and, if so, what is its nature? As suggested in a previous publication, renal failure in the above-mentioned conditions should be defined as functional, because these cases, as has been found by many other authors, display either no pathological changes at all in the kidneys or only changes insufficient to account for the grave functional disturbances. If there are changes, these are more or less of the same character irrespective of whether the fatal uraemia was caused by burns, by crushing injuries or other forms of trauma, or even by pyloric stenosis (Beall, Bywaters, Belsey, *et al.*, 1941; Young and McMichael, 1941; Young, 1942; McLetchie, 1943; Darmady *et al.*, 1944). The tubules are affected, while the glomeruli are generally found to be normal, although the nature of the functional disturbance—oliguria or anuria—points particularly to functional changes in the glomerular apparatus (Fishberg, 1939).

"Extrarenal uraemia," or "functional renal failure," as it may also be called, is closely connected with "extrarenal azotaemia" (Zondek, 1944). The latter term designates only those cases with high non-protein nitrogen in the blood due not to renal failure but to increased endogenous breakdown of protein. The non-protein nitrogen is moderately increased in the blood and markedly increased in the urine (up to 50 g. and more urea per day, thus considerably exceeding the quantity to be expected from the protein intake). The good renal function in these cases is shown also in the ability to secrete urine with optimal urea concentration (up to 5%), and in the satisfactory result of the urea clearance test. The high urea excretion is in marked contrast to a very low excretion of sodium chloride (dissociation of the urea–sodium-chloride excretion). The ratio of sodium chloride to urea in the urine may be 1:20 and even 1:50 and higher. The low excretion of sodium chloride (sometimes less than 1 g. daily) is not limited to the cases with chloride loss due to vomiting, diarrhoea, etc.; it is not caused by hypochloraemia, but is one of the reactions which take place in connexion with the increased breakdown of protein.

There is a definite relationship between extrarenal uraemia and extrarenal azotaemia (Zondek, 1944): (1) extrarenal azotaemia appears under the same morbid conditions as extrarenal uraemia—that is, the same disease which in one person may lead to extrarenal uraemia may cause in another extrarenal azotaemia; (2) in every case of extrarenal uraemia, extrarenal azotaemia is also present. In other words, one patient may react with extrarenal azotaemia alone, whereas the other reacts with extrarenal azotaemia plus renal failure.

Extrarenal Azotaemia

If the increased endogenous breakdown of protein is not on too big a scale there is no rise in non-protein nitrogen in the

blood, but the typical changes in the composition of the urine are present. These cases may be defined as the abortive form of extrarenal azotaemia, and although they are of no particular clinical importance they merit our attention for a better understanding of the main problem. The following two cases are examples of this group:

Case 1.—A man of 30 fell ill with dysentery and a high temperature two days before admission to hospital. On the first day in hospital the blood urea was 46 mg., three days later 36 mg.; NaCl concentration in the urine during this period: 2.1, 2.6, and 2.0 g. per litre, with urea concentration 35, 40, and 42 mg. per 100 ml. Total daily excretion of NaCl ranging from 1.0 to 1.2 g., total urea excretion from 28 to 31 g. Urine free from albumin and other pathological elements.

Case 2.—A man of 38 fell ill one day before admission to hospital with myocardial infarction of the posterior wall. Very slight vomiting and sweating during the first two days. On the second day of his illness there was a moderate rise of temperature, which continued for four days. On admission his blood pressure was 100/70 mm. Hg, falling during the following four days to 90/50 mm. Hg. Blood on the day of admission: NaCl 580, urea 50, and uric acid 3 mg. per 100 ml.; four days later, urea 36 and uric acid 4.2 mg. per 100 ml. Urine during this period: NaCl concentration 2.2–2.6 g. per litre, urea 48–50 g. per litre; total daily excretion: NaCl 1.4–1.8 g., urea 26–30 g. Urine free from albumin, etc.

The occurrence of renal failure is, as already mentioned, a not uncommon event after serious injuries or burns. So far I have had no opportunity of examining such patients; but it is unquestionable that in cases of burns and injuries pure extrarenal azotaemia may be met with. According to Cuthbertson (1936), Lucido (1940), Croft and Peters (1945), in burns at least there is a greatly increased urinary excretion of urea due to abnormal protein breakdown. No attention, however, was paid in these examinations to the sodium chloride excretion; but the latter can be assumed to be very low in these cases. In this connexion the recently published paper of Cooke *et al.* (1945) refers to injuries with "systemic reaction" and presents the findings in the blood and urine of the patients in question. The greatly increased urinary excretion of nitrogen-containing substances is stressed by these authors. The figures for urinary output are sometimes as low as 0.25 g. of chloride daily, while those for total nitrogen reach 20 g. and more. The results of the urine examinations made on various patients were as follows:

Total nitrogen (g.) ..	18·6	18·1	27·9	18·4	25·2	30·5	19·4	27·2
Total chloride (g.) ..	0·25	0·27	1·07	1·82	2·4	4·1	0·62	4·7

Another point of interest is that among these cases with marked dissociation in the excretion of sodium chloride and nitrogen-containing substances there were a number whose blood urea did not increase at all. These findings correspond closely with those described above in such affections as dysentery and myocardial infarction and also represent an abortive form of extrarenal azotaemia.

Extrarenal Uraemia

An essential feature of renal failure which has been observed in cases of uraemia on the basis of primary renal disease is decreased excretion of sodium chloride and urea in the urine. The relationship, however, may be the same as in healthy people. A ratio ranging between 1:1 and 1:4 covers even the variations made possible by the nutritional factor. In cases of extrarenal uraemia the ratio of sodium chloride to urea mostly ranges between 1:10 and 1:20 (Zondek, 1944). There is no need to explain why the urea excretion is not as high in these cases as in pure extrarenal azotaemia, with a ratio varying from 1:20 to 1:50 and even higher. On the other hand, the difference in the sodium chloride and urea excretion found in these cases of extrarenal uraemia is large enough to prove the simultaneous existence of an azotaemic process caused by increased endogenous breakdown of protein. There are, however, extremely severe cases of renal failure which, according to their aetiology, must be considered as belonging to the group of extrarenal uraemia, too, and they behave, so far as the sodium chloride and urea excretion is concerned, like cases of true uraemia due to primary renal disease. But even in these cases the combined pathology of renal failure and extrarenal azotaemia may be assumed, the latter concealed by the severity of the former; the characteristic symptoms of the extrarenal azotaemia may not be revealed until after the lessening or disappearance of the renal insufficiency, as seen in the following case.

Case 3.—A man of 56 developed a very grave form of infectious hepatitis three days before admission to hospital. Besides the usual general symptoms he had severe pains in all his limbs. From the second day of his illness there was constantly increasing jaundice. In its clinical course the disease was very similar to Weil's disease; all bacteriological and serological examinations were, however, negative. In the last 24 hours before admission oliguria was noted, and this became more marked during the following 48 hours; daily urine output not more than 200 ml. On the day of his admission: *blood,* bilirubin (van den Bergh) 8.8 mg. per 100 ml., Takata-Ara ++, cephalin and formol test ++, NaCl 560, urea 223, uric acid 10.5 mg. per 100 ml.; *urine,* traces of albumin, bilirubin +++, urobilinogen +, a few leucocytes and casts, NaCl 2 g. per litre, urea 3.4 g. per litre. The patient was treated with infusions of saline and 5% glucose, and on the fourth day after the beginning of the oliguria diuresis set in; the daily urine output on the following nine days was 1,100–3,000 ml. In spite of the improving diuresis there was a further increase of urea in the blood, reaching its climax of 450 mg. per 100 ml. on the third day of the improved diuresis. From that day onwards continuous fall of the urea. On the ninth day of the improved diuresis, several hours before the patient's death, urea 108 and uric acid 3 mg. per 100 ml. During the whole period the NaCl excretion, in spite of its abundant administration (daily saline infusions of 1,000 ml. for ten days), was very small; its concentration in the urine mostly between 1.3 and 1.9 g. per litre, the daily total between 2 and 5 g. The urea excretion, on the other hand, with the improvement in the diuresis steadily increased: its concentration in the urine between 15 and 32 g. per litre, its daily quantity between 27 and 98 g. The urinary ratio of NaCl to urea of about 1: 2 during the days of the oliguria rose to 1: 15 and 1: 20 after the improvement of the diuresis. On the fourteenth day of his illness the patient succumbed. For the exact data of the case see the Table.

Details of Case 3

April:	8	9	10	11	12	13	14	15	16	17	18
Blood (mg. per 100 ml.):											
Bilirubin		8·8	9·5			13·8			16·3		
NaCl		580						600			
Uric acid		10·5	17·2	14·0	11·0	13·5		6·2	4·6		3·0
Urea		223	283	300	450	380		211	133		108
Urine (g. per litre) ..											
NaCl	2·0	1·8	2·6	1·6	1·3	1·4	1·4	1·8	1·8	1·9	5·7
Urea	3·4	3·5	11·2	15·2	17·6	17·6	28·0	32·8	30·4	28·0	19·2
Urinary excretion daily (g.):											
NaCl	0·4	0·35	2·9	2·9	3·6	3·3	4·8	4·5	5·0	6·7	17·6
Urea	0·68	0·7	12·4	27·3	49·2	40·5	91·2	82·0	85·1	98·0	59·5

Post-mortem Examination (Dr. Karplus).—*Liver:* weight 1,960 g.; macroscopic appearance normal; microscopically, periportal infiltration. *Kidneys:* except for hyperaemia glomerular apparatus entirely normal; Henle's loops without definite findings, but marked changes ranging from degeneration to necrosis in the first and second convoluted tubules.

The fact that after cessation of the oliguria the amount of sodium chloride excreted in the urine remained at its previous low level, while the quantity of urea continuously increased, must be considered proof of the existence of an extrarenal azotaemic process. It might be claimed that the enormous urea excretion was due only to the retention of urea in the body during the anuric stage, but this argument is not justified. The oliguric phase has existed for three days only, during which period the amount of urea retained could not possibly have been large enough to account for a daily urea excretion of from 27 to 98 g. for nine successive days (the exact quantity of the excreted urea during this period amounted to 544 g.). The entire process is not comprehensible except by assuming that there was from the very beginning an enormously increased endogenous breakdown of protein, the detection of which (dissociation of the urinary excretion of sodium chloride and urea) was impossible until the phase of grave renal failure had passed. The patient died in spite of overcoming the renal insufficiency. On the other hand, among the various factors causing the death of the patient, that of protein breakdown should not be neglected. In any case an excretion of more than 500 g. of urea within nine days points to an enormous loss of body protein, and this, it may be stressed, not at the expense of the liver tissue,

the weight of which did not decrease (see the necropsy report). Not always in the group illustrated by Case 3 can the extrarenal azotaemic process be detected after the improvement in the renal failure; as a rule the protein breakdown does not continue for longer than the renal failure, or not for a period sufficiently long to make the proof as clear as in Case 3.

If extrarenal uraemia in the group of diseases quoted in this paper is always associated with extrarenal azotaemia, we may consider the latter (increased endogenous breakdown of protein) to be the cause of the appearance of renal failure. As already suggested by Volhard (1931) in the case of post-operative uraemia, and by Beall *et al.* (1941) and Eggleton (1944) in the case of crushing injuries, the pathological breakdown of protein may lead to the formation of katabolic toxic substances which affect the kidneys and lead to renal insufficiency (nephrotoxic theory of Bywaters). The equally good response of both extrarenal azotaemia and extrarenal uraemia to the same treatment—administration of sodium chloride (Zondek, 1944)—also suggests the interdependence of both processes. However, there may be arguments against this suggestion. Though extrarenal azotaemia is undoubtedly the sequel of protein breakdown, renal failure could be caused by quite another process connected with the primary disease. One factor which should be considered is the fall in blood pressure, another the decreased renal blood flow (Fishberg, 1939), both met with often in the various conditions in question. In animals at least a fall in blood pressure and decreased renal blood flow affect renal function unfavourably, but these two factors can hardly be regarded as responsible for the renal failure in our cases. Thus, in myocardial infarction, a disease characterized by a fall in blood pressure, and probably also by decreased renal blood flow, pure extrarenal azotaemia with very good renal function may be observed (see Case 2). The interdependence between extrarenal azotaemia and functional renal failure should not be overstressed, but their close correlation cannot be doubted.

Discussion

Like symptoms or symptom-complexes appearing in the most different groups of diseases are rightly interpreted as of a non-specific nature. Extrarenal azotaemia should be regarded as such a symptom. It is not the specific nature of a special primary disease which is responsible for this reaction, but rather a factor so far unknown to us and apparently connected with the gravity of a number of different diseases, such as acute enteritis, hepatitis, myocardial infarction, injuries, burns, acute infections, etc. Actually there is no disease which cannot cause extrarenal azotaemia. There is a close relationship between extrarenal azotaemia and functional renal failure, the former being potentially the latter. Given the same basic disease, a person may react, if at all, either with extrarenal azotaemia alone or with extrarenal azotaemia plus functional renal failure—that is, extrarenal uraemia. The range of intensity of the possible reaction is very wide; one end is marked by the mildest form of extrarenal azotaemia, evidenced only by the appearance of the typical changes in the composition of the urine; the other by the most severe form of renal failure with oliguria or even anuria. If with accurate diagnostic methods very slight disturbances in the function of the kidneys should be detected also in cases of so-called pure extrarenal azotaemia, our views would not need to be revised. In these latter cases the extrarenal azotaemic process caused by increased endogenous breakdown of protein would remain the chief factor responsible for the clinical findings. Functional renal failure may also be produced in the absence of an extrarenal azotaemic process; thus katabolic substances other than those from protein katabolism, and exogenous substances (e.g., sulphonamides), may affect the kidneys. But even allowing for this possibility, the vast majority of all cases of functional renal failure may be associated with extrarenal azotaemia. Since extrarenal azotaemia is in these cases non-specific, the accompanying process of functional renal failure must be considered in the same light, though it may be regarded as the specific reaction of the kidneys to a non-specific process—that is, extrarenal azotaemia and what it represents.

The question arises why one patient reacts with extrarenal azotaemia alone and another with extrarenal azotaemia plus functional renal failure. As in many other circumstances a constitutional factor unknown to us may play the decisive part, but other factors must be taken into account. If renal failure is a sequel to the extrarenal azotaemic process, importance must be attached to the intensity of that process. In this connexion it may be recalled that in Case 3, with particularly grave renal insufficiency, the body protein broken down within nine days amounted to nearly 2 kg.; the urea excretion alone, excluding all other nitrogenous substances, was about 550 g., while the protein intake during this period was negligible. The condition of the kidneys before the onset of the disease is another important factor; kidneys affected by arteriosclerosis or damaged by any other chronic disease must be assumed to be more likely to react with renal insufficiency than those of young and healthy people.

If the most different groups of diseases may cause extrarenal azotaemia and functional renal failure, might not the same pattern apply also to primary renal disease? Take the following not uncommon case: A patient has been suffering from an uninfected renal calculus for a long time without any disturbance in the renal function. A sudden infection of the urinary tract may lead to acute uraemia. Might the uraemia not be of the same type as in acute liver affections and in diseases of other specific organs? There is no definite answer to this question as yet, but the following fact is remarkable. The administration of sodium chloride (infusions of saline or saline plus glucose) is an efficient form of treatment in extrarenal azotaemia and extrarenal uraemia, as also in Fishberg's "prerenal" uraemia. There is, too, no better treatment for uraemia in a case of renal calculus, excepting only specific treatment (operation) of the stone itself. The withdrawal of sodium chloride in all renal diseases to the extent to which it was common previously is surely not the right treatment and may even be harmful. We are, however, still very far from being in a position to decide definitely on the indications for its administration in the various renal affections. Our view that uraemia in organic renal disease may sometimes be of the type of extrarenal uraemia—that is, functional renal failure—can serve as a clue to an understanding of the therapeutic efficiency of sodium chloride in at least a special group of cases of renal disease. It is undoubtedly difficult to decide in a specific case of organic renal disease with uraemia whether the renal failure is non-specific—extrarenal and functional in nature—or a specific sequel to the existing organic renal disease. Possibly our examinations may prove helpful in overcoming these difficulties to a certain extent at least. The detection of an extrarenal azotaemic process (marked dissociation of sodium chloride and urea excretion) would permit us to regard the existing renal failure as of extrarenal and functional character, and might prompt us to try sodium chloride therapy, provided there is no definite contraindication. A case belonging to this group and successfully treated with sodium chloride has been reported (Zondek, 1944).

Knowledge of increased breakdown of body protein as the cause of extrarenal azotaemia has been stressed by Croft and Peters (1945) and has prompted in cases of burns a diet rich in protein. I leave open the question whether this line of treatment can be successfully applied in any case of extrarenal azotaemia. Let us bear in mind, however, that extrarenal azotaemia contains in itself the potentiality of renal failure, and it remains to be seen whether or not the development of the latter might be affected by any excessive administration of protein.

Summary

Extrarenal azotaemia is caused by increased endogenous breakdown of protein and brings about an increase of urea and other nitrogen-containing substances in the blood, with a simultaneous excretion of great quantities of urea and small quantities of sodium chloride in the urine (dissociation of the sodium chloride and the urea excretion).

There is also an abortive form of extrarenal azotaemia, the changes in the composition of the urine being the only abnormality found.

There is a connexion between extrarenal azotaemia and extrarenal uraemia.

Extrarenal azotaemia and extrarenal uraemia are non-specific symptom-complexes which may be produced by a variety of diseases or injuries.

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PULMONARY EXCHANGE DURING ARTIFICIAL RESPIRATION

BY

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AND

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The relative merits of the various methods of artificial respiration have long been a subject of dispute, and each of them still has its advocates. This lack of agreement is doubtless due mainly to the fact that in ordinary circumstances it is impossible to compare the efficiency of the various procedures. In any real emergency skilled personnel and scientific recording apparatus are rarely available. In any event, the prime object must be the resuscitation of the victim; if the method used is successful it is deemed to be a good one, but if the patient dies it is assumed that he was beyond saving.

It is true that the volume of air passing in and out of the lungs in artificial respiration has been recorded, but the value of the conclusions reached is doubtful. For the considerable anatomical differences between man and other mammals make the conclusions reached on the latter largely inapplicable to man. Experiments on man are valueless unless the volunteer is unconscious, toneless, and not breathing. Yandell Henderson (1938) confirms that the tonus of the respiratory muscles of the conscious subject varies so that the respiratory minute volume is kept almost constant, whatever the method used and whatever the rate of the chest movements. A warm cadaver might furnish figures of value, but the means is open to obvious objection, and any experiments carried out after rigor mortis had set in would be useless.

One of our colleagues (E. A. P.) felt that the various methods of artificial respiration could and should be evaluated on a subject depressed to simulate a victim *in extremis*. He asked to be anaesthetized profoundly and brought to respiratory arrest. Artificial respiration now became essential, since almost the only evidence of life was that the heart-beat continued. The various methods of artificial respiration were tried in turn, and the pulmonary exchange recorded on a kymograph.

The subject was a healthy young man of about 10 st. (63.5 kg.). The larynx was anaesthetized with cocaine, after which anaesthesia was induced with pentothal and continued with ether and air from an "Oxford vaporizer." A wide-bore oral endotracheal tube was passed, and the space between it and the trachea occluded with the usual inflated cuff. This ensured that all the air passing in and out of the lungs was measured on a recording spirometer. The apparatus for measuring pulmonary ventilation was in charge of Dr. S. L. Cowan, D.Sc., lately physiologist to this department, and it is hoped that details will be published by him in due course. The kymographic records which we give here are of the better-known methods of artificial respiration, and the ones which we think will be of most general interest. Subsequently the experiments were repeated on another colleague (J. R.), of about 13 st. (82.5 kg.) weight.

The subjects were deeply anaesthetized until the intercostal muscles were paralysed. At this stage slight hyperventilation resulted in respiratory arrest. Various methods of artificial respiration were carried out by the same skilled operator. The respiratory rate was kept uniform at 10 per minute.

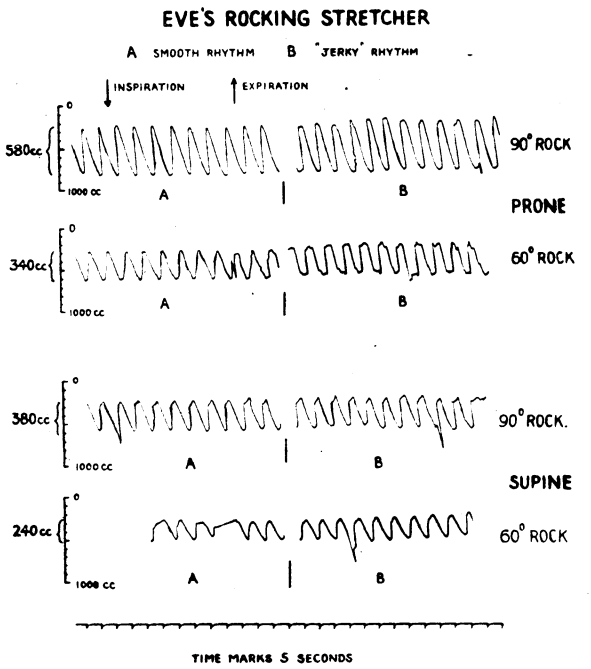

FIG. 1

Fig. 1 shows that Eve's (1943) rocking method produces a larger tidal exchange with the subject on his face than when on his back. The reason for this is not clear. Ventilation of the lungs increases with the angle through which the subject is rocked. Fig. 2 shows the figures resulting from Schäfer's and

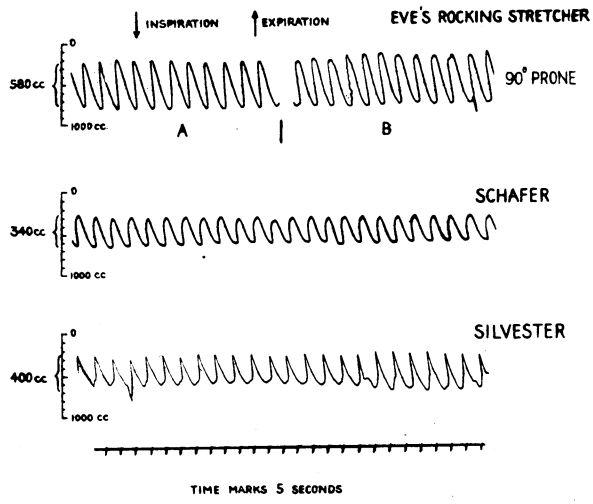

FIG. 2

Silvester's methods compared with those obtained from rocking the prone subject through 90°. In Fig. 3 the figures for inflation of the lungs with oxygen from an Oxford inflator (Macintosh and Pratt, 1939) give an accurate indication of the value of this method. In the "mouth-to-mouth" method the operator blew into the free end of the endotracheal tube. The term "mouth to mouth" is here, therefore, a misnomer, and the figures are