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ALTERATIONS IN THE DIURNAL EXCRETION OF ELECTROLYTES DURING INTERMITTENT POSITIVE-PRESSURE RESPIRATION

BY

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The diurnal variations in the excretion of water and electrolytes by the kidney have been studied extensively, the most important contributions to the literature having been listed by Stanbury and Thomson (1951) in an account of their own observations. These authors found the excretion per minute of water and of sodium, potassium, chloride, and bicarbonate ions falls during the night together with the urinary pH, whereas the output of ammonia and titratable acid rises. These diurnal excretory rhythms are extremely resistant to attempts to alter their pattern. Thus, starvation, water deprivation for three days, salt deprivation for nine days, the sustained action of deoxycortone acetate and antidiuretic hormone, and the temporary disturbance of the sleep rhythm do not abolish the excretory rhythm (Stanbury and Thomson, 1951).

On the other hand, hyperventilation for periods of 15 to 40 minutes disrupts the excretory rhythm, causing an increased excretion of sodium, potassium, and bicarbonate ions with little change in the excretion of chloride (Brown, Campbell, Elam, Gollan, Hemingway, and Vischer, 1949; Stanbury and Thomson, 1952). This last observation suggests that the nocturnal reduction in the excretion of these electrolytes may be due to the raised alveolar CO₂ tension which develops at night (Mills, 1953). On the other hand, Longson and Mills (1953) found that the maintenance of a raised alveolar CO₂ tension by the inhalation of 5 to 6½% CO₂ for three hours in the morning failed to prevent the matutinal rise in the excretion of electrolytes. Hence, though it is tempting to attribute the variations in the excretory rhythm of electrolytes to changes in respiration, the evidence is at present conflicting.

The maintenance of human subjects on intermittent positive-pressure respiration (I.P.P.R.) for long periods

during the treatment of respiratory paralysis has provided an opportunity for further investigation of this problem, the results of which are presented here. This method of artificial respiration permits respiration to be maintained at a constant rate, pressure, and tidal volume by day and by night for long periods; hence the variations in these factors which constantly occur during normal respiration are eliminated. Because patients being thus treated are usually recumbent and variations in the renal excretion of electrolytes during acute changes of posture have been reported (Wilkins, Bradley, and Friedland, 1950), observations on the effects of prolonged recumbency on the diurnal excretory rhythms are reported first.

Material and Methods

Observations on the effects of recumbency were made serially on one subject before, during, and after recumbency, and single observations were made on four other subjects, two of whom were totally paralysed by motor neurone disease, after varying periods of recumbency. The effect of I.P.P.R. was observed in six subjects after varying periods of artificial respiration. The urine was obtained by inserting an indwelling catheter and collecting urine at midnight, 6 a.m., 8 a.m., 10 a.m., 12 noon, 2 p.m., 4 p.m., and 12 midnight. The patients were recumbent and capable of little physical exertion apart from slight movements of the arms. They kept a normal ward routine, sleeping from about 10 p.m. to 6.30 a.m. and taking food by mouth or by nasal tube at the usual meal-times. The respiratory minute-volume was maintained at a level suitable for the patient, and its constancy was checked at frequent intervals throughout the period of collection of urine by passing the expired air through a gas-meter. The sodium and potassium ionic content of the urine was estimated by flame-photometer, and the chloride by a potentiometric method (Sanderson, 1952).

Effect of Recumbency

A male patient aged 28 years with an anxiety state, who complained of intolerable fatigue, was glad to lie recumbent for 21 days. He remained flat in bed, lying on his back, or on either side, but not sitting up. Two estimations, one of which is shown in Fig. 1, were made before he was confined to bed, and showed a normal diurnal pattern for the excretion of sodium, potassium, and chloride. Estimations were made on days 1, 2, 4, 7, 9, 13, and 21 of the recumbent period, but no alteration in the diurnal pattern was observed (Fig. 1). Two further estimations after he resumed activity again showed a normal pattern.

In view of the absence of change with a short period of recumbency, single estimations were made on four other patients. K. T. had disseminated sclerosis and had been in bed for 21 days. D. C. had a prolapsed intervertebral disk, and estimations were made on the 14th and 21st days of recumbency; and J. C. and M. had motor neurone disease and had been in bed and totally paralysed for 17 months and 2 years respectively. All showed normal diurnal excretory patterns (Fig. 2).

Effect of I.P.P.R.

In only two of the six patients on I.P.P.R. was it possible to observe the type of diurnal excretory pattern of electrolytes before treatment was instituted. Both had normal patterns, and, as the remaining four patients

FIG. 1.—Excretion in $\mu\text{Eq}/\text{min.}$ of Na, K, and Cl in a normal patient before, during, and after a 21-day period of recumbency. Abscissa is marked in six-hour periods starting from midnight, excretion from midnight to 6 a.m. being in black.

were healthy until stricken acutely by a muscle-paralysing disease, there is no reason to believe that they did not have a normal diurnal excretory pattern. J. P., who was on I.P.P.R. for only five days, showed no change in his diurnal excretory pattern. The first change observed in L. S., A. T., C. C., and V. B. was in the excretion of potassium, where a flattening of the tide appeared at a time when the tides of sodium and chloride were unchanged. This is illustrated on the 25th day in C. C., 14th day in L. S., and 21st day in A. T. in Fig 3.

The change was effected by the nocturnal output per minute of potassium rising and the daytime output per minute falling until the excretion per minute was approximately equal by day and by night. The time of onset of this change varied, being present by the seventh day in L. S. and A. T. C. C. was not examined between the 6th and 25th days; the change was present by the latter date and, apart from one narrow peak, there was a suspicion that the change was developing on the sixth day. It was difficult to determine the exact time of appearance of the change in relation to the onset of I.P.P.R. in V. B. because, though the change was present by the third day of continuous treatment, the patient had been treated intermittently over the previous four weeks. In the sixth case, J. C., there was no evidence of flattening of the diurnal excretory pattern of potassium after 28 days' treatment, when I.P.P.R. was discontinued.

The second change in the excretory pattern developed some time later and consisted of a flattening in the chloride tide—illustrated by day 105 in C. C. and by

FIG. 2.—Excretion in $\mu\text{Eq}/\text{min.}$ of Na, K, and Cl in four patients who had been recumbent for varying periods. Scale for D.C. is $\times 0.5$; for M it is $\times 5$.

FIG. 3.—Excretion in $\mu\text{Eq}/\text{min.}$ of Na, K, and Cl in four patients on I.P.P.R. for varying periods. Scales are $\times 1$ except C.C. day 4, Na $\times 10$, Cl $\times 3$; day 6, Na $\times 10$; L.S. day 2, Na $\times 5$, Cl $\times 5$; V.B. day 3, Na and K $\times 5$, Cl $\times 100$; A.T. day 7, K $\times 5$, day 21, K $\times 3$.

day 23 in L. S. (Fig 3). The final change, illustrated by day 23 in L. S., consisted of a flattening in the tide of sodium. The time of onset of the changes in sodium and chloride is hard to ascertain. Both were present by day 23 in L. S. C. C. was not examined between day 105 and day 277, the change in the sodium pattern being present on the latter date.

An important observation in relation to a possible explanation of the change in the diurnal excretory pattern is the total daily output of the various electrolytes. These are set out in the Table, which shows

Total Daily Excretion of Na, K, and Cl in mEq and Serum K in mEq/100 ml. in Four Patients on I.P.P.R.

Patient	Day of I.P.P.R.	Total Daily Output			Serum K
		Na	K	Cl	
C. C.*	4	2.1	48.9	10.4	—
	6	3.6	70.3	53.0	4.2
	25	56.0	57.0	50.0	4.8
	49	81.0	83.0	67.0	—
	105	142.0	92.0	115.0	—
L. S.	2	19.5	27.7	17.7	3.2
	6	90.0	33.0	63.0	3.6
	14	23.5	23.0	23.5	—
	23	135.0	69.0	114.0	4.4
A. T.	7	35.2	8.9	21.3	4.6
	21	49.1	37.4	47.1	—
V. B.	1	21.0	28.0	1.6	4.5

* This patient was receiving supplements of KCl

that at the onset of I.P.P.R. treatment all patients were excreting extremely small amounts of sodium, potassium, and chloride, but later the daily output approached normality. This was probably due to the fact that at the time of induction of I.P.P.R. the patients had become acutely ill and were deficient in both water and electrolytes. These deficiencies were corrected and a rise in the electrolyte excretion followed.

Discussion

The occurrence of diurnal rhythms in bodily functions is not surprising in view of the fact that we are, in general, active by day and at rest by night. One important question is whether these rhythms are inherent in the organism or whether they are determined by external environmental influences. It has in fact been shown that these rhythms are to some degree susceptible to changes in life's routine. Thus Norn (1929) showed that excretory tides were reversed in those who habitually worked by night and slept by day. More recently Lewis and Lobban (1957a) demonstrated in two groups of people living in the Arctic Circle, on 21-hour and 27-hour "days," that the excretory rhythms gradually adapted to the abnormal time routines. The present results in the recumbent patients indicate, however, that variation in physical activity is not the operative factor maintaining or adjusting the rhythms, for the rhythms were clearly present during strict recumbency and even after many months of total paralysis. This does not, of course, prove that the rhythms are inherently determined, for even the totally paralysed patients cannot be regarded as existing under completely basal conditions throughout the 24 hours, for they slept by night and fed by day. It may be that this minimal variation in their daily routine was the sufficient factor for the maintenance of their tides.

When attention is turned to the factors which abolish the tides it is immediately clear from the results with the recumbent patients that the changes in the patients on

I.P.P.R. were not due either to their recumbency or to their muscular paralysis. The observations of Evans, Jones, Milne, and Steiner (1954), that potassium depletion abolishes the diurnal excretory rhythm of this electrolyte, makes it also necessary to consider this possibility, especially as patients on I.P.P.R. tend to be hyperventilated and hyperventilation induces potassium loss. The prolonged output of normal amounts of potassium in the urine and the normal serum potassium levels indicate that potassium depletion was not present in the patients, hence it cannot be advanced as the cause of the abolition of the tides.

The fundamental difference between the recumbent and the I.P.P.R. groups was that the former breathed unaided whereas respiration in the latter was controlled with regard to rate, pressure, and tidal volume. Hence it is not unreasonable to suggest that the factor which abolishes the tides is the fixed respiration throughout the 24 hours. How this is achieved is not clear. It could be that fixed respiration acts by its effect on gaseous exchange: on the other hand, it may act by its effect upon pressure relationships within the thorax. Thus Love, Roddie, Rosensweig, and Shanks (1957) have shown that breathing against a rapidly pulsatile pressure increases urine flow and the output of solutes, though breathing against a constant positive pressure had no influence on urine flow or solute output. A further consideration is the observation of Rosenbaum, Ferguson, Davis, and Rossmel (1952) that the administration of cortisone abolishes or reverses the excretory tide of potassium and those of sodium, chloride, and water to a less severe degree. It may be, therefore, that fixed respiration acts primarily upon adrenocortical secretion and through this influences the diurnal excretory rhythms. It is not possible to decide among these various possibilities on the basis of the present evidence.

Two further points are worthy of comment. The first is that the tides show great inertia to change. This was noted by Lewis and Lobban (1957a) in their experiments, complete adaptation to abnormal time routines rarely being complete even after six weeks. The present results confirm this, the first change in the potassium tide not being present before at least six days of continuous treatment. This clearly rules out any sudden adjustment of acid-base or intrathoracic pressure relationships as being responsible for the abolition of the tides.

The second point worth comment is that dissociation between the various rhythms undoubtedly occurs. Lewis and Lobban (1957b) observed dissociation between potassium on the one hand and water and chloride on the other hand, the potassium under the conditions of their experiment being the more resistant to change. The present results confirm that dissociation between the various excretory rhythms is possible, though in this instance potassium was the first to change, the chloride and sodium rhythms following later. It is clear, therefore, that different mechanisms are responsible for the various tides.

Summary

The diurnal excretory tides of potassium, sodium, and chloride during periods of recumbency up to two years were unaltered in five patients.

Periods of intermittent positive-pressure respiration of seven days or more flattened first the excretory tide of

potassium in four out of five cases, and later those of sodium and chloride.

Possible mechanisms altering the diurnal tides are discussed.

I wish to thank Mr. J. L. MacNaughton for technical assistance.

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TUBERCULOSIS CONTROL IN DENMARK

BY

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During a recent visit to Denmark I attempted to assess the significance of the differences between the tuberculosis statistics in that country and those in England and Wales.

The decline of tuberculosis in Denmark has been much faster and has gone much further than in England and Wales. This could be due to differences in (a) population and environment, (b) notification criteria, and (c) the actual measures adopted for controlling the disease in the two countries.

General environmental conditions such as diet, housing, rest, and recreation, are equally good in both countries; the long dark winters of Denmark should outweigh on balance the adverse factor of atmospheric pollution in England.

There have been no tuberculous cattle in Denmark since 1951, and the three-yearly routine tuberculin tests performed on all cattle have revealed only an insignificant number of positive reactors infected from human or possibly avian sources.

Denmark is less industrialized than Britain, and has a population of under 4½m. Except in Copenhagen, there is less opportunity for an infected person to pass on his bacilli at work, at play, or when travelling. The Copenhagen incidence rates are actually almost twice as high as the rates for all Denmark and, as shown in the Table, are more comparable with those for the County of Essex.¹ The rates in England vary locally to an even greater extent,² the extremes in 1956 being Gateshead with 216 and West Suffolk with 22 per 100,000 of the population.

The keeping of a Central Tuberculosis Register in Denmark does much towards preventing duplication. Each notification is checked at the central register against a list of the tuberculous population, and also

New Cases of Respiratory Tuberculosis Notified Annually Per 100,000 of Population

Year	All Denmark	England and Wales	Copenhagen	Essex
1947 ..	85	100	146	98
1948 ..	80	101	154	93
1949 ..	68	102	116	88
1950 ..	58	96	98	87
1951 ..	56	97	82	85
1952 ..	48	95	74	82
1953 ..	40	93	64	72
1954 ..	35	84	66	62
1955 ..	28	76	56	49
1956 ..	25	70	47	49

against a separate list which is maintained of all names that have been discarded from the register on account of cure, emigration, or inability to examine for three successive years. A double-entry system is used to lessen the chance of duplication due to discrepancies in identification particulars.

Relapse is defined as recurrence after freedom from symptoms without treatment for three years or more, and 14% of positive-sputum diagnoses in Denmark in 1955 come into this category. The inadvertent inclusion of such cases in the British incidence figures as new cases could have a considerable effect on the statistics. As the proportion of notifications among the higher age groups increases, so will the chances of duplicate notification increase, since older people are more likely to have had a previous infection, and to have forgotten a notification of long ago, or to have some personal or family reasons for wishing to conceal it.

According to the Danish Tuberculosis Index, less than 3% of tuberculosis deaths had missed notification during life. In England and Wales, however, out of a total of 4,853 deaths from respiratory tuberculosis in 1956, no fewer than 1,244 (26%) are reported as not previously notified.² Might not a number of these cases have been notified in another area or under another (for example, maiden) name during life, thus appearing twice in the incidence statistics?

It would obviously be very difficult to maintain a central tuberculosis register for all England and Wales, because of the large population and incidence. Regionalized checking and recording, however, would be more likely to prevent duplication than our present system of accepting notifications from a very large number of local unrelated sources.

When comparing the total known cases of respiratory tuberculosis in the two countries (in 1955) it is found that in England and Wales they represent 691 per 100,000 of the population,³ but only 6.3% of these were known to be sputum positive at that time; in Denmark the total cases on the registers amounted to only 304.5 per 100,000 of the population, but 25.5% of these were known to be "open" cases, comprising 17.2% with positive sputa and 8.3% with positive stomach washings.

In Denmark about 90% of all notified cases of respiratory tuberculosis are confirmed at some stage by positive bacterial culture, compared with 41% in this country.³ The bacillus is diligently sought in every case, several sputa and stomach washings being cultured, if necessary. In Copenhagen 30% of the new cases are confirmed by culture of stomach washings, these being cases in which no sputum is obtainable. During 1956 a total of 50,000 sputa and 20,000 stomach washings were sent from all parts of Denmark to the Central Laboratory in Copenhagen for culture, and about 10% of these were positive.