THE NATRIURESIS OF FASTING: RELATIONSHIP TO CHANGES IN PLASMA RENIN AND PLASMA ALDOSTERONE CONCENTRATIONS

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SUMMARY

1. The relationship of changes in plasma renin and plasma aldosterone concentration to electrolyte balance was studied during total fasting and during sodium deprivation followed by total fasting.

2. During simple sodium deprivation obese subjects lost significantly more sodium than lean subjects, but the rise in plasma renin concentration (PRC) was similar in the two groups.

3. During total fasting there was a failure of PRC to increase in the expected manner despite a marked negative sodium balance. In the early stages of the fast, PRC decreased in nine of eleven subjects while subsequently it increased in all subjects.

4. During sodium deprivation PRC and plasma aldosterone concentration (PAC) rose in all subjects studied, but in the first few days of a period of total fasting immediately following, there was a fall in PRC in eight of ten subjects studied, while PAC continued to rise in five of six subjects in whom it was measured.

5. These results are discussed in relation to the concept of the renin-angiotensin system as a regulator of aldosterone secretion.

Both obese and lean subjects excrete more sodium while fasting than when maintained on a low sodium diet (Gamble, Ross & Tisdale, 1923; Hervey & McCance, 1952; Bloom & Mitchell, 1960; Rapoport, From & Hudsan, 1965; Bloom, Azar & Clark, 1966). Stinebaugh & Schloeder (1966) separated the effects produced by salt restriction from those of fasting, by feeding their subjects low sodium diets immediately prior to total fasting. They showed that there was a natriuresis associated with the withdrawal of calories, which began on the second day of fasting, reached a peak on the fourth day and then subsided. This natriuresis associated with the withdrawal of calories, which occurs at varying levels of sodium intake (Bloom, 1962;
Veverbrants & Arky, 1969) is arrested by carbohydrate or by protein refeeding (Bloom, 1962; Katz, Hollingsworth & Epstein, 1968), but not by fat alone (Haag, Reidenberg, Shuman & Channick, 1967). Indeed some workers have found that fat refeeding temporarily aggravates the natriuresis (Veverbrants & Arky, 1969).

Despite intensive investigation the cause of the natriuresis has not been established. Suggested mechanisms include solute diuresis (Hervey & McCance, 1952; Harvey & Lasker, 1963) keto-acidosis (Gamble et al., 1923) and changes in aldosterone secretion (Rapoport et al., 1965).

There have been several studies of plasma renin activity and urinary aldosterone excretion during fasting (Rapoport et al., 1965; Hansen, Horlyck, Gronbaek & Iverson, 1967; Haag et al., 1967; Verdy & de Champlain, 1968; Katz et al., 1968; Smith, Ross & Marshall-Jones, 1969), but there has not been, as far as we are aware, any systematic attempt to relate changes in plasma renin and plasma aldosterone concentrations, either to the natriuresis of fasting or to the sodium retention of refeeding; nor have these changes been compared directly with those found in sodium deprived subjects. The present experiments were therefore undertaken with these aims in view. A preliminary account of this work has been given recently (Chinn, Brown, Fraser, Lever & Robertson, 1969).

**METHODS AND MATERIALS**

All blood samples were taken between 09.00 and 09.30 hours with the patient recumbent; PRC was estimated by an enzyme kinetic technique (Brown, Davies, Lever, Robertson & Tree, 1964a). With this method, replicate estimations from a stock plasma pool had a mean value of 24.97 units/l (SD 3.98 units, n = 62). Replicates varied less when estimated in the same batch as was the case with the majority of subjects in the study (SD 2.07 units/l) (Brown, Chinn, Dusterdieck, Fraser, Gleadle, Lever, Robertson & Tree, 1969a). PAC was estimated by a modification of the double isotope derivative technique (Fraser & James, 1968). Replicate estimations from a stock plasma pool during the course of these experiments had a mean value of 11.56 ng/100 ml and an overall range of 10.24-13.10 ng/100 ml (SD 0.83, n = 12).

Plasma cortisol was measured in three patients by a similar technique (Fraser & James, 1968). Serum electrolytes were estimated in the routine biochemistry laboratory using the Technicon AutoAnalyser. Blood sugar was measured by the ferri-cyanide technique on the AutoAnalyser.

The obese subjects studied were clinically free from endocrine disease. All the patients in the study weighed at least 35% more than the upper limit of their desirable weight as obtained from tables prepared by the Metropolitan Life Insurance Company (1960) (see Davidson & Passmore, 1963). Patients were encouraged to be fully ambulant throughout the study. Fluid intake was unrestricted though measured, and during periods of total fasting only water or unsweetened milkless tea was permitted. Urine was collected over 24-h periods, the volume measured, and aliquots taken for estimation of sodium and potassium using a Technicon AutoAnalyser Mark III flame photometer. It was extremely uncommon for bowel motions to occur during total fasting and faecal electrolytes were not measured. Patients were weighed each morning between 08.00 and 09.00 hours on an Avery beam balance. Blood pressure was measured daily before rising. Since no consistent change was noted during fasting blood pressure will not be referred to in the results section.
Plasma renin and aldosterone during fasting

Study

**Study 1.** Total fasting

**Study 2.** Na⁺ Deprivation

**Study 3.** Na⁺ Deprivation, Total fasting, Refeeding

Fig. 1. Protocols of the three studies.

**Protocol of the studies** (see Fig. 1)

There were three studies:

1. Total fasting in eleven obese subjects (all females).
2. Sodium deprivation in eight normal subjects (six males, two females).
3. Sodium deprivation followed by total fasting and refeeding in ten obese subjects (two males, eight females).

In Study 1, 10 days fasting was preceded by a basal period of 3–5 days during which the patients ate a normal ward diet.

In Study 2, eight normal (lean) students were given a diet containing 8–10 mEq sodium and 46–65 mEq potassium for 5 days. Results in six of these normal subjects have been reported previously (Brown, Davies, Lever & Robertson, 1964b).

In Study 3, ten obese subjects were given a diet of 600–1000 kcal value containing 0–10 mEq of sodium for 5 days. Seven of these subjects received 35–46 mEq potassium during this period while the other three subjects received no potassium, since for reasons of expediency their diet consisted of Hycal (Beecham). This period of sodium deprivation was immediately followed by 12 days of total fasting and then by 5 days of refeeding with a diet of 400–600 kcal value containing 100–125 mEq sodium and 30–46 mEq potassium. It should be noted that the three subjects fed with Hycal were both sodium and potassium deprived prior to fasting, but since the results followed the same pattern as in the other seven subjects, the results for the two groups have been analysed together.

**RESULTS**

**Study 1: Total fasting in obese subjects** (see Fig. 1)

All subjects lost weight, the heaviest tending to lose most weight and most sodium. Total weight loss was positively correlated both with initial weight \( r = +0.84, P < 0.001 \) and with cumulative sodium loss \( r = +0.76, P < 0.01 \). The weight loss for the 10-day period varied from 4.4 to 9.5 kg with a mean of 7.1 kg.

Urinary sodium loss persisted throughout the fast (Fig. 2). Despite this, in nine of eleven...
subjects PRC at first decreased and then rose markedly towards the end of the fast (Fig. 2).

Other changes during the fast included continued, although diminishing, urinary potassium loss, hypokalaemia, and a decreased serum $\text{Tco}_2$ and blood sugar (Table 1). The serum concentrations of sodium and chloride did not change significantly (Table 1).

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Study 2: Sodium deprivation in lean and obese subjects (see Fig. 1)

Sodium deprivation of both lean and obese subjects led to a smaller urinary sodium loss and a greater rise in PRC (Fig. 3) than did fasting. Moreover, sodium deprivation in the obese produced a greater sodium loss ($t = 3.22, P<0.01$) than in the lean subjects. The rise in PRC was smaller in the obese than in the lean subjects although this difference did not reach statistical significance (Fig. 3). Thus PRC rose most in the subjects losing least sodium.
**Plasma renin and aldosterone during fasting**

**Table 1.** Urine potassium, serum electrolytes and blood sugar at different stages of total fasting

<table>
<thead>
<tr>
<th>Total fasting</th>
<th>Control</th>
<th>Day of fasting</th>
<th>1</th>
<th>4</th>
<th>9</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urine K (mEq/24h)</td>
<td>—</td>
<td>42±3.5</td>
<td>39±4.1</td>
<td>18±2.8</td>
<td></td>
</tr>
<tr>
<td>Serum K (mEq/l)</td>
<td>4.1±0.07</td>
<td>3.9±0.09</td>
<td>4.0±0.08</td>
<td>3.6±0.10**</td>
<td></td>
</tr>
<tr>
<td>Serum Na (mEq/l)</td>
<td>140±0.79</td>
<td>139.7±1.45</td>
<td>140±1.14</td>
<td>140.8±0.88</td>
<td></td>
</tr>
<tr>
<td>Serum Cl (mEq/l)</td>
<td>103-0±0.67</td>
<td>103.0±0.61</td>
<td>102.8±0.80</td>
<td>100.8±1.01</td>
<td></td>
</tr>
<tr>
<td>Serum TC02 (mEq/l)</td>
<td>24.4±0.56</td>
<td>22.7±0.67</td>
<td>19.7±0.66***</td>
<td>17.6±0.93***</td>
<td></td>
</tr>
<tr>
<td>Blood sugar (mg/100 ml)</td>
<td>82±2.3</td>
<td>69.2±4.7*</td>
<td>54.0±2.3***</td>
<td>57.5±3.1***</td>
<td></td>
</tr>
</tbody>
</table>

Mean values ± 1 SEM

* Mean values differing from initial value by t-test with P<0.05
** P<0.01
*** P<0.001

**Study 3:** Sodium deprivation followed by total fasting and refeeding in obese subjects (see Fig. 1)

**Weight**

The mean initial weight of the ten subjects studied in this group was 93.1 kg with a range of 82.3–112.4 kg. The mean weight loss during the period of sodium deprivation was 3.49 kg.
with a range of 1.65–5.05 kg while the mean weight loss during the total fast alone was 6.08 kg (range 4.0–9.5 kg). As in Study 1, the weight loss during total fasting alone was positively related to the weight of the patient at the beginning of fasting \((r = +0.76, P < 0.01)\). The total weight loss during sodium deprivation and total fasting taken together, was also related to initial weight \((r = +0.77, P < 0.01)\). However, when the period of sodium restriction was considered separately the association between weight loss and initial weight was not significant \((r = +0.24, P > 0.1)\). Nor was the weight loss occurring during sodium deprivation significantly related to cumulative sodium loss \((r = +0.08, P > 0.5)\). The relationship seen between cumulative sodium loss and weight loss during total fasting in Study 1 was not significant in this series \((r = +0.31, P > 0.2)\).

**Urinary electrolytes**

**Sodium**: The mean changes in sodium balance for the six subjects in whom both plasma renin and plasma aldosterone concentrations were measured are shown in Fig. 4. Urinary sodium excretion had fallen to below 20 mEq/day in eight out of ten patients by the fifth day of sodium deprivation. Following this during the early days of fasting, all subjects showed an increase in urinary sodium excretion. Thereafter, this again fell to very low levels in all but one patient. There was very marked sodium retention in all ten patients studied during the first few days of refeeding. The mean cumulative loss was 186 mEq (range 60–404 mEq) during sodium deprivation and 173 mEq (range 95–298 mEq) during the 12-day fast. The mean total cumulative loss for the two periods was thus 359 mEq. During the first 3 days of refeeding there was a mean sodium gain of 290 mEq (range 230–311 mEq). This represented retention of 92% of the sodium intake. In 6 patients who were followed during 5 days refeeding, the mean cumulative sodium gain was 476 mEq (range 364–513 mEq) representing retention of 91% of intake.

**Potassium**: On average the ten subjects lost 55 mEq of potassium (range +90 to −171 mEq) during 5 days sodium deprivation and 345 mEq (range 223–483 mEq) during the fast. The positive potassium balance occurred in only one patient and we have no explanation for it. In the first 3 days of refeeding they gained 69 mEq (range 46–98 mEq) and in six patients after 5 days refeeding there was a mean gain of 131 mEq (range 95–170 mEq) of potassium.

**Serum electrolytes and blood sugar**

The period of study has been divided arbitrarily into four sections: (1) basal and period of sodium deprivation; (2) first 5 days of fasting; (3) last 7 days of fasting; (4) period of refeeding. Electrolytes were estimated on at least one occasion in every patient during each of these periods and usually more frequently (up to four times/period). The mean of the estimations carried out in each period was used as representative of the electrolyte measurements in that period. Table 2 shows the results for the group. It is interesting to note that unlike Study 1 the serum sodium concentration showed a significant decrease during the first 5 days of fasting. This might be related to the preceding period of sodium deprivation. Otherwise, results were similar to those obtained in Study 1. Blood sugar was considered in the same way and results shown in Table 2 were similar to those in Study 1.

**Plasma renin concentration**

PRC increased during sodium deprivation in all subjects in whom a measurement of renin was obtained in the basal period (Table 3); then, in eight of ten subjects during the subsequent
fast, it decreased, while in the other two subjects (Table 3, Nos. 3 and 6) it showed little or no change despite the urinary loss of sodium. At a later period during the fast, PRC again increased in all subjects (Table 3). Although the timing varied from case to case, this pattern of change, shown in marked form in the subject illustrated in Fig. 5, was also apparent in the group as a whole (Fig. 4).
**Plasma aldosterone concentration**

PAC increased during sodium deprivation in all six subjects in whom it was measured (Table 3, Figs. 4 and 5). In the early stages of the subsequent fast, four out of six cases (Table 3, Nos. 1, 5, 8, 10) showed a further rise of PAC, at a time when PRC was decreasing. Higher PAC values were found on the third, fourth, sixth and ninth days of fasting (Table 3, Fig. 5), but on the twelfth day of fasting aldosterone showed a decrease in five of the six cases. Refeeding led by the fourth day to a large decrease in PAC in each of the five subjects studied in this way.

**Relationship between PRC and PAC**

In all six subjects studied, PRC and PAC increased during sodium deprivation. During the later stages of fasting and in the refeeding period, changes in PRC were accompanied by similar changes in PAC. However, during the first 5 days of fasting PRC and PAC clearly dissociated since as PAC continued to increase, PRC decreased (Table 3, Fig. 5). This also is shown by a significant change in the correlation coefficient of PRC and PAC during the first 5 days of fasting (from \( r = +0.48, n = 12 \) during sodium deprivation to \( r = -0.32, n = 27 \) during the first 5 days of fasting, \( P<0.03 \), returning to \( r = +0.38, n = 19 \) during the later stages of fasting and the refeeding period), although in themselves none of these coefficients reached statistical significance.

**DISCUSSION**

**Value of fasting in the treatment of obese patients**

The present study confirms the value of short periods of total fasting in achieving rapid weight loss, thus providing encouragement for the obese patient to persist with low calorie diets. The long term success of such a regime, however, remains in question, since despite close
## Table 3

Plasma renin concentration (units/l) and plasma aldosterone concentration (ng/100 ml) during sodium deprivation, fasting and refeeding.

<table>
<thead>
<tr>
<th>Subject</th>
<th>Sodium deprivation</th>
<th>Fasting</th>
<th>Refeeding</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>R</td>
<td>A</td>
<td>R</td>
</tr>
<tr>
<td>1</td>
<td>7.0</td>
<td>11</td>
<td>27.5</td>
</tr>
<tr>
<td>2†</td>
<td>*</td>
<td>*</td>
<td>30.0</td>
</tr>
<tr>
<td>3†</td>
<td>7.5</td>
<td>9</td>
<td>16.6</td>
</tr>
<tr>
<td>4†</td>
<td>23.6</td>
<td>14</td>
<td>40.5</td>
</tr>
<tr>
<td>5</td>
<td>7.6</td>
<td>5</td>
<td>27.2</td>
</tr>
<tr>
<td>6</td>
<td>*</td>
<td>*</td>
<td>45.0</td>
</tr>
<tr>
<td>7</td>
<td>17.6</td>
<td>*</td>
<td>20.5</td>
</tr>
<tr>
<td>8</td>
<td>11.9</td>
<td>16</td>
<td>20.0</td>
</tr>
<tr>
<td>9</td>
<td>10.8</td>
<td>*</td>
<td>16.2</td>
</tr>
<tr>
<td>10</td>
<td>7.1</td>
<td>14</td>
<td>22.0</td>
</tr>
</tbody>
</table>

**Mean:** 11.6 11.5 27.7 35 23.3 40 20.9 65 25.8 78 24.7 90 31.1 104 36.6 96 40.0 74 25.4 38 24.3 13 10.6 33 15.9 6

**SD:** 6.0 4 9.6 10 10.2 9 11.3 45 17.0 44 16.1 37 17.4 70 16.8 65 179 81 10.6 33 15.9 6

**SEM:** 2.1 2 3.2 4 3.2 4 3.6 18 5.7 18 5.4 15 5.5 31 6.4 29 5.7 33 3.8 15 5.6 3

* = not measured, † = potassium deprived, R = renin (normal range 4-20 units/l), A = aldosterone (normal range <18 ng/100 ml)
follow-up by the dietician, many of the present patients regained at least some of the weight lost in fasting during the first 3 months after discharge. The long-term results of fasting regimes have been fully discussed by Harrison & Harden (1966) and MacCuish, Munro & Duncan (1968).
Plasma renin and aldosterone during fasting

Previous studies of renin and aldosterone during fasting and refeeding

Verdy & de Champlain (1968) found that plasma renin activity rose during fasting in a manner similar to the rise produced by sodium deprivation, and concluded that it seemed likely that the renin-angiotensin system played a role in the conservation of sodium during fasting. Our results do not support these observations since we found that there was failure of normal stimulation of plasma renin during the early days of fasting when sodium was being lost in the urine in considerable quantities and, overall, the increase in PRC during fasting was significantly less than during sodium deprivation in obese subjects (Fig. 3).

Haag et al. (1967) found in one patient that plasma renin activity had reached levels on the seventeenth day of fasting equivalent to those found in normal patients sodium deprived for 3 days. The authors concluded that the renin-angiotensin system was able to respond only partially to the stimulus of a decreased plasma volume during fasting. It should be remembered, however, when interpreting the above results that plasma renin activity is not equivalent to plasma renin concentration (Brown, Davies, Lever & Robertson, 1966).

There have been several studies of urinary excretion of aldosterone and of aldosterone secretion rate during fasting and refeeding (Rapoport et al., 1965; Haag et al. 1967; Katz et al., 1968; Verdy & de Champlain, 1968). Results have been conflicting. Katz et al. (1968), for example, found that the urinary excretion of aldosterone was not consistently altered by starvation or refeeding, whereas Verdy & de Champlain found the urinary excretion of aldosterone was elevated in three out of four subjects at the end of a 7-day fast. Walker, Cooke & Turin (1969) showed that retention of sodium during refeeding following a 4-week fast was not associated with a raised aldosterone secretion rate, but that the secretion rate fell to low levels after 3 days of refeeding, despite continuation of sodium retention for a further 7 days. This is in agreement with our own studies, in which both plasma renin and aldosterone concentrations fell during the refeeding period. The finding of Verdy & de Champlain (1968) of a very marked rise of aldosterone excretion in one patient during glucose refeeding, might be explained by the fact that this patient was being refed with a low salt diet while our patients and those of Walker et al. (1969) were refed with diets of normal sodium content. However, Haag et al. (1967) found a rise in aldosterone excretion in two patients who were refed with a diet containing 88 mEq of sodium per day.

It is also possible that plasma aldosterone concentration might remain unaffected despite a raised aldosterone secretion rate, if for instance the metabolic clearance rate of aldosterone was proportionately increased.

Three components of the sodium loss of fasting

The present study confirms that obese fasted subjects excrete more sodium than either lean or obese sodium deprived subjects who are given an adequate calorie intake. This apparently excessive loss of sodium during total fasting has been demonstrated in many previous studies (Gamble et al., 1923; Hervey & McCance, 1952; Bloom & Mitchell, 1960; Rapoport et al., 1965; Schoeder & Stinebaugh, 1965; Bloom et al., 1966; Garnett, Ford, Golding, Mardell & Whyman, 1968) and has been intensively investigated. Stinebaugh & Schoeder (1966) by sodium depriving their subjects prior to total fasting, showed that there were two components to the sodium loss of fasting: an exponentially decreasing loss attributable to simple sodium deprivation as demonstrated by Strauss, Lamdin, Smith & Bleifer (1958), and a secondary
natriuresis related to the complete withdrawal of calories. Using a similar technique this has been confirmed in the present study. Steinbaugh & Schloeder also showed that the cumulative sodium loss during a period of sodium deprivation and during a period of total fasting immediately following, was approximately equal to the cumulative sodium loss occurring during a similar period of total fasting without prior sodium depletion. This has also been confirmed in the present study. Finally, the results of the present investigation suggest that the sodium loss occurring in simple sodium deprivation is exaggerated in obese subjects, thus adding a third component to the natriuresis of fasted obese subjects. *(Vide infra.)*

**Mechanism of the secondary natriuresis**

The secondary natriuresis could be accounted for in several ways. There could be, for example, a net sodium loss from the extracellular compartment with or without a subsequent drain from the intracellular fluid. Alternatively, there could be an influx of sodium into the extracellular fluid from some other source. In this instance the extracellular fluid would be expanded, and the urinary sodium loss would be a consequence of the expansion.

The natriuresis has been generally regarded as a net loss of sodium from the ECF although Bloom (1962) did suggest that the pattern of sodium excretion during fasting was indicative of a sodium surfeit rather than deficit. The results of the present study support this conclusion. The fall in plasma renin concentration during the secondary natriuresis found in the present study is suggestive of a response to a sodium load as is observed in certain other conditions where there is sodium retention (Brown *et al.*, 1964b; Brown, Chinn, Davies, Dusterdieck, Fraser, Lever, Robertson, Tree & Wiseman, 1968b). Thus during total fasting there may be an influx of sodium to the ECF with consequent expansion of the plasma volume, depression of plasma renin concentration and excretion of the excess sodium, represented by the secondary natriuresis. Plasma volume has been measured during fasting on several occasions (Rapoport *et al.*, 1965; Bloom, Azar & Smith, 1966; Hansen *et al.*, 1967), but in all instances the measurement was made too late to detect any changes which might have occurred in the first 2 or 3 days of fasting.

Garnett *et al.* (1968) have shown that following a fall during the first week of total fasting the total exchangeable sodium rises progressively and they have suggested that sodium in bone is made available for exchange under conditions of total starvation. The natriuresis of fasting occurs early, however, often beginning on the first day, and if bone were providing sodium to the ECF it is unlikely that there would be a fall in exchangeable sodium during the early days of fasting, such as that demonstrated by Garnett *et al.* As already mentioned Bloom (1962) found that when fasting patients were given sodium supplements, although the sodium was not quantitatively excreted during the period of intake, the urinary sodium excretion increased significantly above the preceding fasting levels, and continued for several days after supplements ceased. These findings are suggestive of a response to sodium surfeit rather than deficit, although as will be discussed, the changes in plasma aldosterone concentration in the present study are not in accord with this idea.

Other possible sources of an influx of sodium during fasting include the gut (McCance, 1969, personal communication) and the intracellular fluid. The gut might well provide an immediate source of sodium by the release into the circulation of sodium in the various intestinal juices. Approximately 1000 mEq of sodium are secreted into the gut per 24 h (Black, 1967) and
presumably a portion of this is always present within the gut in dynamic equilibrium with the ECF. With the onset of fasting, the volume of sodium containing intestinal juice might be reduced and sodium would be reabsorbed into the ECF. The converse state certainly occurs in animals after a meal, when plasma volume contracts and plasma renin increases (Blair-West & Brook, 1969).

Another possibility is that during the metabolic acidosis of fasting, hydrogen ions might enter the cells in exchange for sodium ions, which would then enter the extracellular fluid and be excreted during the natriuresis of fasting, but as far as we are aware intracellular pH and sodium concentration have not been studied under these circumstances. The timing of the events is rather against this possibility in that the natriuresis usually occurs early before the metabolic acidosis is established.

It is well known that injected renin and angiotensin modify urinary sodium excretion (see Bock, Brown, Lever & Robertson, 1968) and it is therefore possible that endogenous renin and angiotensin also act as renal hormones capable of altering sodium excretion. Thus a fall in renin (and presumably angiotensin) such as occurred in the present study might contribute to the natriuresis. We have discussed in another context the possibility that an increase in renin (and angiotensin) could produce both an antinatriuresis and antidiuresis (Brown, Chinn, Lever & Robertson, 1969b). Finally, it has recently been shown that the presence of bicarbonate in the interstitial fluid of the rat kidney is essential for efficient reabsorption of sodium in proximal tubules (Rumrich & Ullrich, 1968; Stein, Rector & Seldin, 1968). In fasting it may well be that during the metabolic acidosis bicarbonate concentration in the interstitial fluid is lowered, as it is in the plasma, with consequent depression of proximal tubular reabsorption.

The dissociation between renin and aldosterone

In many clinical and experimental circumstances plasma renin levels and aldosterone values change in the same direction (Genest, de Champlain, Veyrat, Boucher, Tremblay, Strong, Koiv & Marc-Aurele, 1964; Fraser et al., 1965, 1966, 1969; Laragh, Sealey & Sommers, 1966). While these observations lend support to the concept that the renin-angiotensin system might be a regulator of aldosterone secretion (Gross, 1958), in most situations it remains to be shown that the observed changes in renin are quantitatively sufficient to account for the alterations in aldosterone (Brown, Fraser, Lever & Robertson, 1968a). Indeed, Boyd, Adamson, James & Peart (1969) have suggested that in man some factor other than angiotensin is involved in the increase in PAC produced by dietary sodium deprivation. However, Miller, Vander, Kowalczyk & Geelhoed (1968), have shown that sodium deprivation in the dog is associated with increases in plasma renin activity which are within the range capable of causing changes in aldosterone excretion. A distinct dissociation between renin and aldosterone has been noted under certain circumstances in the sheep (Blair-West, Cain, Catt, Coghlan, Denton, Funder, Nelson, Scoggins, Wintour & Wright, 1968a), and in man (Fraser, James, Brown, Davies, Lever & Robertson, 1966; Slater, Tuffley, Williams, Beresford, Sonksen, Edwards, Ekins & McLaughlin, 1969). The present studies have shown a further dissociation. It is of interest that this occurred at one stage only during the fast—in the secondary natriuresis. By contrast during sodium deprivation, in the later stages of fasting and in the refeeding period, the relationship between plasma levels of renin and aldosterone was closer. Before discussing explanations for this dissociation between renin and aldosterone, the possibility that there is no dissociation between angiotensin and aldosterone should be considered. More angiotensin (and there-
fore more aldosterone) might be produced by a given amount of renin during early fasting. There is no evidence for or against this possibility in the present studies, but in other situations variations in the efficiency of the renin/angiotensin/aldosterone system, mainly due to changes in renin substrate concentration, have been suggested (see Brown et al., 1966; Helmer & Judson, 1967; Newton, Sealey, Ledingham & Laragh, 1968; Skinner, Lumbers & Symonds, 1969; Weir, Paintin, Robertson, Tree, Fraser & Young, 1970).

There are several possible explanations for a true dissociation. Firstly, during the secondary natriuresis something other than angiotensin may stimulate aldosterone secretion. Factors known to stimulate aldosterone production include the potassium ion (Blair-West et al., 1968a; Bartter, Mills, Biglieri & Delea, 1959; Cannon, Ames & Laragh, 1966; Moran, Rosenberg & Zimmermann, 1959; Muller, 1965; Wright, 1963), ACTH (Bartter, Barbour, Carr, Delea & Slater, 1964; Binnion, Davies, Brown & Olichney, 1965; Liddle, Duncan & Bartter, 1956; Ganong, Biglieri & Mulrow, 1966; James, Landon & Fraser, 1968), hyponatraemia (Blair-West, Coghlan, Denton, Goding, Wintour & Wright, 1963a; Davis, Urquhart & Higgins, 1963) and the ammonium ion (Muller, 1965; Blair-West, Coghlan, Denton, Goding, Wintour & Wright, 1968b). The potassium ion is well recorded as being a stimulus to aldosterone secretion and since potassium is released by the catabolism which occurs during total fasting (Drenick, Blahd, Singer & Lederer, 1966) it must be considered as a possible factor stimulating aldosterone secretion in this situation. However, in the present studies serum potassium levels did not show an increase at any time during fasting and fell markedly in the later stages, thus making potassium a rather unlikely stimulus to aldosterone secretion under these circumstances.

ACTH also seems to be an unlikely stimulus since no evidence was obtained of its increased secretion. Plasma cortisol concentration measured in three patients was at no time increased above the limit of the normal range, an observation in agreement with previous studies (Schachner, Wieland, Maynard, Kruger & Hamwi, 1965; Garces, Kenny, Drash & Taylor, 1968; Sabeh, Alley, Robbins, Narduzzi, Kenny & Danowski, 1969; Kolanowski, Pizarro, de Gasparo, Desmecht, Harvenet & Crabbé, 1970). Plasma cortisol concentration has been widely used as an index of pituitary function (Landon, James & Stoker, 1965; Landon, Wynn & James, 1963; Greenwood, Landon & Stamp, 1966) and while it is obviously less satisfactory than direct measurement of plasma ACTH concentration, in most cases it provides an acceptable indirect guide. However, it has recently been shown by Fragachan, Nowaczynski, Bertranav, Kalina & Genest (1969) that dehydroepiandrosterone (DHA) inhibits 11β-hydroxylation *in vivo* in the dog, and since plasma levels of DHA have been shown to increase markedly during the first 7 days of fasting in obese subjects (Hendrikk, Heyns & de Moor, 1968) it is possible that in these circumstances plasma cortisol is not a true index of ACTH secretion. In fact ACTH levels might be very high in a vain attempt to stimulate increased cortisol secretion during the stressful situation of total fasting. Against this it must be noted that 11β-hydroxylation also occurs in the biosynthesis of aldosterone, and effective 11β-hydroxylase inhibition would be expected also to interfere with the formation of aldosterone. In the ox there is in fact evidence *in vitro* that DHA interferes with 11β-hydroxylation of DOC to corticosterone (Sharma, Forchielli & Dorfman, 1963) and that *in vivo* it also interferes with both cortisol and aldosterone synthesis. Moreover, in man, Sabeh et al. (1969) showed that fasting produced partial blockade of 11β-hydroxylase. The marked rise in plasma aldosterone in the present studies argues against any serious quantitative interference with aldosterone synthesis. While the absence of a rise in
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Cortisol suggests that the rise in aldosterone was not due to ACTH, for the reasons stated this cannot be entirely excluded.

Perfusion of the adrenal cortex with isotonic glucose increases aldosterone secretion independently of changes in angiotensin (Blair-West et al., 1963a; Davis et al., 1963). Hyponatraemia per se might thus stimulate aldosterone secretion. However, in the present study hyponatraemia did not develop although there was a small fall in serum sodium during the early days of fasting.

There is no evidence that changes in the pH of the plasma affect aldosterone secretion, but it is thought that the ammonium ion may stimulate aldosterone under certain circumstances. As urinary excretion of ammonium and therefore perhaps also the plasma level, rises markedly during fasting, although not until the third day (Rapoport et al., 1965), the ion may play some part in the behaviour of renin and aldosterone.

Another explanation of the dissociation is that the aldosterone stimulating effect of renin and angiotensin is enhanced during fasting. Blair-West, Coghlan, Denton, Goding, Wintour & Wright (1963a) and Fraser, Brown, Chinn, Lever & Robertson (1969) have shown that increased stimulation of aldosterone production by angiotensin may occur in the presence of a sodium deficit.

A further possibility is that the increase in plasma aldosterone concentration simply represents a fall in the metabolic clearance rate (MCR) of aldosterone. However, preliminary studies in this laboratory suggest that changes in MCR during fasting are not sufficient to account for the rise in plasma aldosterone concentration.

Failure of raised plasma aldosterone concentration to prevent the natriuresis

Another question raised by the present study is why, in the face of a rising plasma aldosterone concentration in the early days of fasting, urinary sodium excretion increases. Two of the factors already discussed might be involved. Firstly, if angiotensin promotes sodium reabsorption by a renal action, then a fall in angiotensin might cause an excessive load to be presented to distal tubules where aldosterone might be unable to cope with the increased amount. Secondly, the necessity for the presence of bicarbonate for efficient sodium reabsorption in proximal tubules has been demonstrated in the rat by Rumrich & Ullrich (1968) and Stein et al. (1968). Since serum bicarbonate is decreased in fasting, often markedly, its concentration in the interstitial fluid in the kidney may also be lowered. This might decrease proximal tubular sodium reabsorption and thus be a second factor in contributing to an increased sodium load in distal tubules. It may be significant that when renin eventually rises in fasting the natriuresis ceases. Another possibility is that the response of the renal tubular cells to aldosterone is decreased in the early days of fasting. There is good evidence of varying sensitivity to sodium retaining steroids in several experimental conditions (Davis, Johnston, Howards & Wright, 1967). Finally, there may be a change in the balance between aldosterone and a natriuretic hormone, as yet undefined. It is interesting that Hendrikx et al. (1968) have found that plasma levels of dehydroepiandrosterone (DHA) a substance with natriuretic activity (Williamson, 1965), increase during the first 7 days of fasting while urinary excretion falls sharply. Plasma levels then gradually decrease. The first 7 days of fasting is the period in which the natriuresis occurs despite markedly raised plasma concentration of aldosterone.

The natriuresis cannot in the present studies be due to a rise in blood pressure, since as mentioned no significant change in blood pressure occurred.
Exaggerated sodium loss during simple sodium deprivation in obese subjects

One of the most striking features of this study was the finding that obese subjects appear to conserve sodium less well than lean subjects during a short period of simple sodium deprivation (see Fig. 3). An explanation of this finding is not immediately apparent. One factor which must be taken into account is that the obese subjects were eating a restricted amount of calories during the period of sodium deprivation (600–1000 kcal) while the normal (lean) subjects were not. However, a preliminary study of obese subjects sodium deprived but given a calorie intake of 1500–1750 kcal suggests that this is not the explanation. Another possibility is that obese subjects normally have a higher sodium intake than lean subjects, i.e., that they are in a state of mild sodium loading. If obese subjects were sodium loaded to any extent one might expect their plasma renin concentration to be lower than that of subjects in normal sodium balance. However, the mean plasma renin concentration in these patients while eating a normal ward diet and shortly after their admission to hospital was, if anything, higher than that of the lean subjects studied. Thus sodium loading does not appear to affect explanation of the phenomenon.

In conclusion, the present study poses more questions than it answers. It confirms the exaggerated sodium loss in obese fasted subjects and suggests that it may have three components: exponentially decreasing sodium loss due to simple sodium deprivation; an exaggeration of this loss peculiar to obese subjects; and a secondary natriuresis related to withdrawal of calories. It is not known whether this secondary natriuresis is also exaggerated by obesity. The secondary natriuresis occurs in the face of a rising plasma aldosterone concentration which paradoxically occurs while the plasma renin concentration is decreasing. It is suggested that the natriuresis may in part be attributable to this fall in plasma renin concentration although other factors have been considered.

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