ESCAPE FROM SODIUM AND POTASSIUM RETAINING ACTIONS OF ASPIRIN-LIKE DRUGS USED IN A PATIENT WITH BARTTER'S SYNDROME

YASUHIRO ISHIKAWA, M.D. AND TAKAO WADA, M.D.

Escape from sodium and potassium retaining actions of aspirin-like drugs used in a patient with Bartter's syndrome.

An analysis was done with regard to the mode of escapes from sodium and potassium retaining actions of aspirin-like drugs in a patient with Bartter's syndrome. In the indomethacin therapy of the syndrome, there was a delay in the initiation of potassium escape as compared to sodium escape, whereas no delay was seen in the ibuprofen therapy. This delay was probably related to the direct or indirect inhibition of sodium-potassium exchange in the distal nephrons. The course of aspirin therapy went midway between the above two. In the spironolactone therapy, the mode of escape was a mirror image of the one in the indomethacin therapy. Also, in a patient with rheumatoid arthritis, but without Bartter's syndrome, the escapes from the effects of indomethacin were seen. In order to understand the effect of these drugs on potassium excretion in Bartter's syndrome, some other intrarenal events, such as the influence on chloride transport in the loop of Henle leading to potassium conservation, may have to be considered.

THERE are a number of studies to suggest that prostaglandins are among the substances which modulate sodium excretion (UNaV). Prostaglandins may stimulate the release of renin from the kidneys,[1-5] and inhibit the tubular reabsorption of sodium.[6-8] In addition to their effects on the kidney, prostaglandins may also stimulate the production of aldosterone directly.[9,10] These properties of the prostaglandins suggested that they could play a central role in the pathogenesis of Bartter's syndrome. In fact, results of studies from several laboratories showed that the patients with Bartter's syndrome had abnormally high plasma levels or high urinary excretion of prostaglandin E, A or F.[11-16] Furthermore, indomethacin, an inhibitor of prostaglandin synthesis, has been found to be effective to correct the major disturbances of the syndrome.[11,12,14-16]

Ibuprofen, which is structually different from indomethacin but which inhibits prostaglandin systhetase as well, was reported to be similarly effective in a case of Bartter's syndrome.[12] Although all of these findings support the central role of prostaglandins in pathogenesis of the syndrome, there are also important observations which do not favor the above notion. For example, the administration of indomethacin or ibuprofen did not produce a sustained correction of hypokalemia of the syndrome in spite of the

Key Words:
Bartter's syndrome
Escape
Indomethacin
Prostaglandins

(Received on January 26, 1979; Accepted on May 28, 1979)
Department of Internal Medicine, School of Medicine, Keio University, Tokyo, Japan
All correspondence including reprint requests should be addressed to Dr. Takao WADA, Department of Internal Medicine, School of Medicine, Keio University, 35 Shinanomachi, Shinjuku-ku, Tokyo, Japan.

TABLE I THE BASE LINE LEVELS, WITH THE PATIENT SUPINE, OF PRA, AI, AII, PAC AND PGE AS COMPARED TO THE CONTROLS

		Case E. Y.	*Normal Controls (Mean ± SD, N = 30)*
PRA	*ng/ml/hr*	*5.8 – 8.5*	*1.4 ± 1.0*
AI	*pg/ml*	*4,250 – 6,230*	*1,740 ± 1,130*
AII	*pg/ml*	*240 – 432*	*98 ± 46*
PAC	*pg/ml*	*356 – 395*	*123 ± 80*
PGE	*pg/ml*	*850 – 1,260*	*720 ± 330*

sustained suppression of prostaglandin production[11,12] Thus its seems that one should closely reexamine the effects of the so-called prostaglandin inhibiting drugs on Bartter's syndrome.

MATERIALS AND METHODS

Patient

A 28 year old man (E. Y.) was referred to the Saitama Social Insurance Hospital following 2 years history of muscle weakness, general fatigue, polydipsia and polyuria. He had no diarrhea, no vomitting and no history of taking diuretics or cathartics. Thus there was no evidence of large fecal potassium loss. He was admitted to the hospital on July 27, 1975. Physical examination revealed a well developed man with normal mental acuity. His weight was 65 kg and his height 170 cm. Blood pressure was 112/70 mmHg. The urine was normal. The hematocrit was 51 percent; the white cell count was 6900, with 56 per cent neutrophils, 6 per cent band forms, 27 per cent lymphocytes, 9 per cent monocytes and 2 per cent eosinophils. Urea nitrogen was 15.7 mg/dl, creatinine 1.2 mg/dl, uric acid 7.5 mg/dl, total cholesterol 196 mg/dl. Blood pH was 7.42, bicarbonate 24 mEq/L, potassium 2.0 mEq/L, sodium 132 mEq/L, chloride 90 mEq/L, calcium 8.8 mq/dl, phosphate 2.3 mg/dl, and magnesium 1.7 mg/dl. Creatinine clearance was 106 ml/min, PSP excretion 45% in 15 minutes. Roentgenologic studies including an intravenous pyelography did not show any abnormalities.

As a control to this patient, a 40 year old man (H. S.) with rheumatoid arthritis was chosen. He had no abnormal findings except those related to rheumatoid arthritis.

Fig.1. The renal biopsy specimen of Case E. Y. showing juxtaglomerular hyperplasia.

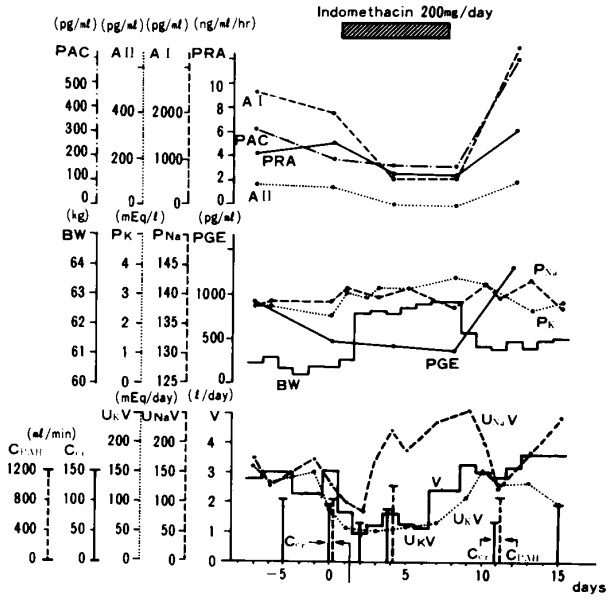

Fig.2. The effects of indomethacin given to Case E. Y.

Methods

In short-term studies the patient was placed on a 200 mEq sodium, 100 mEq potassium diet and ad libitum fluids. Plasma samples were obtained with the patient supine in the early morning. Daily 24-hour urine collections were obtained for analysis of sodium, potassium and creatinine. Plasma renin activity (PRA), a plasma angiotensin I (A I), plasma angiotensin II (A II), and plasma aldosterone (PAC) were measured by radio-immunoassay according to modifications of the methods of Haber et al., Goche et al., and Bayard et al.;[17–19] performed by the Special Research Laboratory, Tokyo. Plasma prostaglandins were measured by radio-immunoassay according to modifications of the procedures of Jaffe, Levine, Caldwell and Hickler.[20–23] The measurements of plasma prostaglandin E (PGE) and F1α (PGF1α) were performed by the Special Research Laboratory and those of plasma prostaglandin A (PGA) by the Ono Pharmaceutical Company, Tokyo.

Long-term studies were performed over eight months. Because of the lengthy period the patient was allowed to stay home and go to work as usual. Although the intake of sodium and potassium could not be strictly controlled, its rough constancy was monitored through the occasional collections of 24-hour urine samples. The patient was requested to appear, in the early morning, at the outpatient clinic of the Saitama Social Insurance Hospital regularly. Control studies on the patient of rheumatoid arthritis (H. S.) were done with the same protocols as in the patient with Bartter's syndrome except that he took 50 mEq of potassium daily.

RESULTS

Diagnosis of Bartter's syndrome (Patient E. Y.).

Urinary excretion was very high (near 100 mEq/day) even under the hypokalemic condition. As shown in Table I, base line levels, with the patient supine, of PRA, A I, A II, PAC and PGE were significantly increased as compared with the normal controls. The patient exhibited marked resistance to the pressor effect of angiotensin, requiring 120 ng/kg/min for 20 mmHg rise in diastolic blood pressure. A renal biopsy specimen showed marked juxtaglomerular hyperplasia (Fig. 1). No medullary tissue was found in the specimen.

Thus the obtained data were all consistent with the diagnosis of Bartter's syndrome.

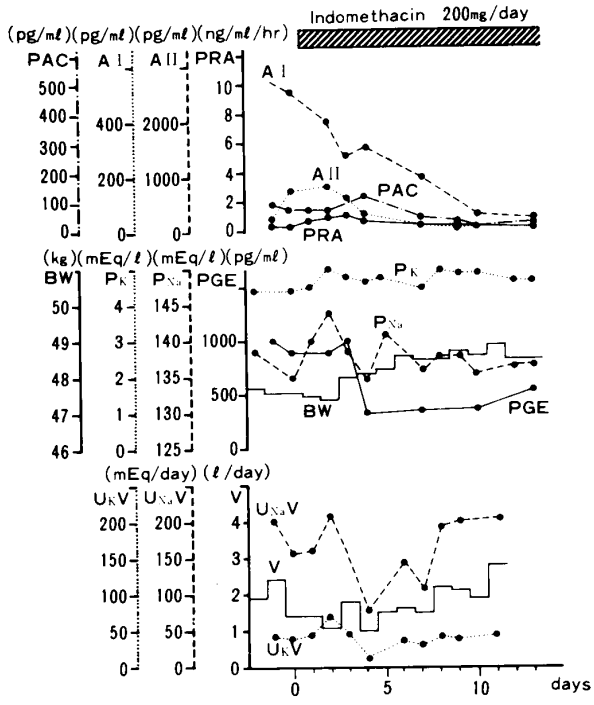

Fig.3. The effects of indomethacin given to a control subject (Case H. S.)

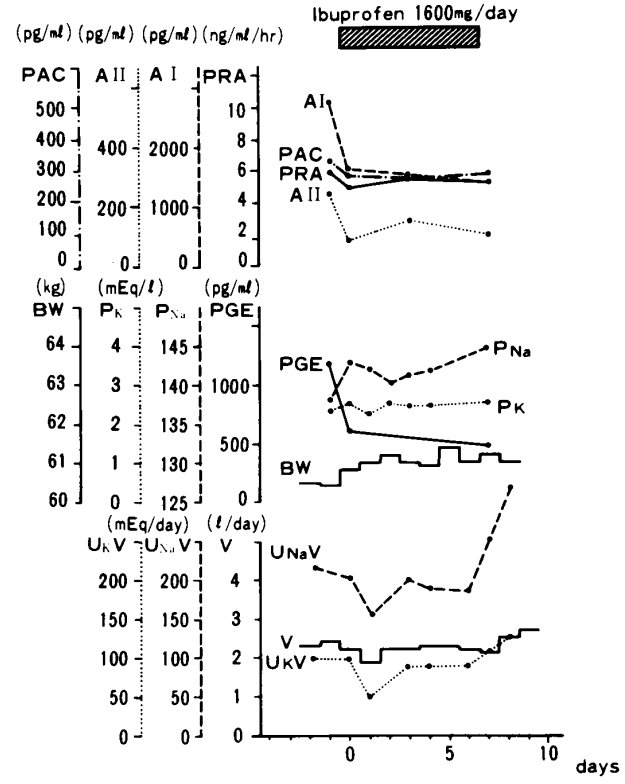

Fig.4. The effects of ibuprofen given to Case E. Y.

Response to Indomethacin (Figures 2 & 3)

The administration of 200 mg/day of indomethacin resulted in a striking decrease in urinary sodium from 180 mEq/day to 80 mEq/day, accompanied by simultaneous falls of PRA, A I, A II, PAC and PGE (Figure 2). PGF1α and PGA roughly parallelled to PGE. Namely, PGF1α decreased from 940 pg/ml on the day 0 to 300 pq/ml on the day 7, and it rebounded to 5250 pg/ml on the day 11, the fourth day after the withdrawal of indomethacin. PGA also decreased from 7.8 ng/ml on the day 0 to 4.6 ng/ml on the day 7 and returned to 7.2 ng/ml.

While all of the hormonal variables including prostaglandin levels, were staying suppressed, sodium excretion (UNaV) began to increase on the third day of indomethacin therapy. Because of this, the body weight stopped increasing to make a plateau. This sequence of events may well be called an escape phenomenon. Interestingly enough, potassium excretion (UKV) rapidly fell from 100 mEq/day to 40 mEq/day and maintained this level, in spite of the prompt return of UNaV to its initial level. This phenomenon apparently points to the inhibitory effect of this drug on sodium-potassium exchange in the renal tubules, which without doubt contributed to raise plasma potassium from 2.2 mEq/L to 3.4 mEq/L.

The change of GFR, estimated from endogeneous creatinine clearance did not seem to explain the escape phenomenon. Nevertheless, the movements of GFR must be noted since it should have somehow reflected intrarenal hemodynamic changes. Coincident with the administration of indomethacin GFR fell and remained low throughout the treatment. It may seem strange that PRF, estimated from C_{PAH}, did not fall at that time. However, it is very likely that our protocol missed to catch the initial phase of decrease in PRF. PRF seem to have recovered thereafter, and have even exceeded the initial level. This dissociation between GFR and PRF may have changed hydrostatic pressure or oncotic pressure in the postglomerular capillaries eventually to inhibit the sodium reabsorption.

In the control patient with rheumatoid arthritis, the effect of indomethacin appeared in a slightly different way (Figure 3). UNaV initially increased with the start of the drug, but soon began to decrease. It reached the bottom level on the fourth to fifth day, and regained its rising tendency toward the initial level. This second increase of UNaV helped to halt the increase of

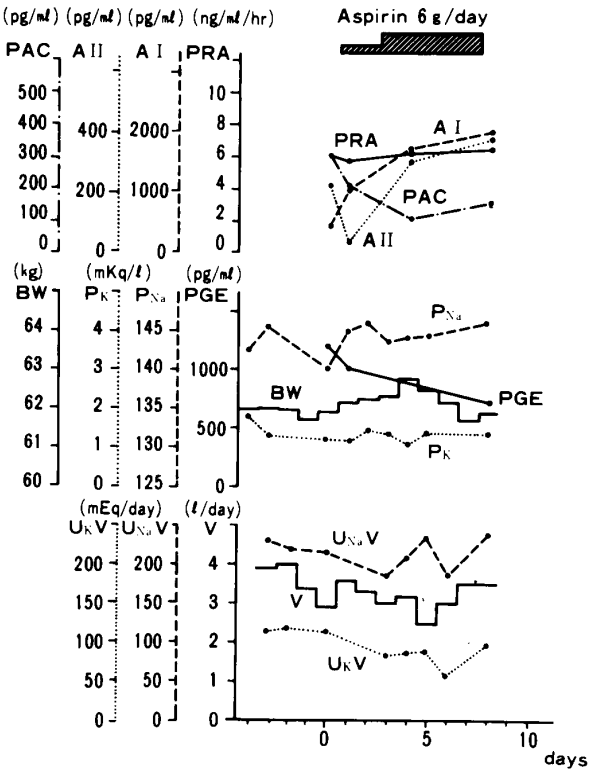

Fig.5. The effects of aspirin given to Case E. Y.

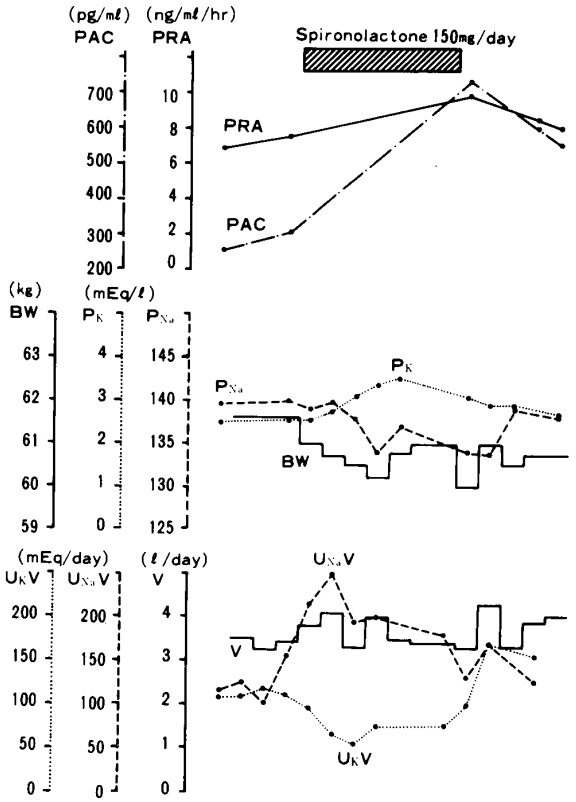

Fig.6. The effects of spironolactone given to Case E. Y.

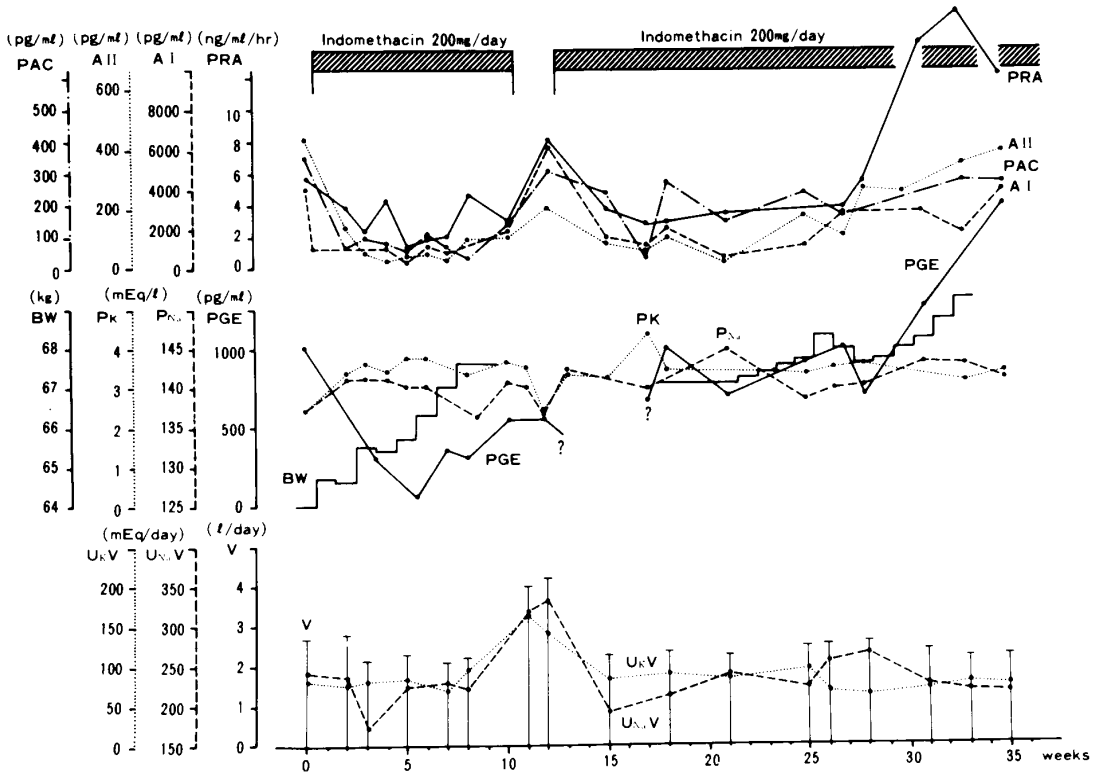

Fig.7. The prolonged effects of indomethacin given to Case E. Y.

the body weight at a certain level. Thus the escape phenomenon occurred in this control patient as well.

Response to Ibuprofen (Figure 4)

Treatment with ibuprofen, 1600 mg/day, gave rise to transient falls of UNaV and UKV in concert with the fall of PRA, A I, A II, PAC, and PGA (Fig. 4). (PGF1α was also lowered from the initial value of 1100 pg/ml to 239 pg/ml by the one week administration of this drug.) In spite of the sustained suppression, thereafter, of all of these hormonal variables, UNaV began to increase as in the case of indomethacin therapy. However, the behavior of UKV was unique at this time. It apparently followed the movements of UNaV, and thus indicated that the sodium-potassium exchange was not inhibited by ibuprofen. The body weight increased by 2 kgs above the control value and kept that level throughout the treatment.

Response to Aspirin (Figure 5)

Taking side effects of aspirin into consideration, the full amount of the drug was not started at the beginning of the study. The dose was increased stepwise from 2 to 6 g/day during the period of this test. UNaV fluctuated because of this, although it roughly followed the response pattern seen in the studies with other prostaglandin inhibiting agents. Even under the sustained suppression of PGE as well as PRA, A I, A II and PAC, UNaV tended to return to the initial value. Also, PGF1α decreased from 483 pg/ml to 320 pg/ml by the administration of aspirin for one week. Although UKV remained suppressed, plasma potassium level was not normalized.

Response to Spironolactone (Figure 6)

Unfortunately, plasma samples for PGE as well as A I and A II were not obtained in this study. From the point of view of the homeostasis, however, the attitude of the kidney at that time is worth being commented.

The pattern of UNaV depicted the mirror image of that in the indomethacin treatment. As can be seen, UNaV once increased from 120 mEq/day to 250 mEq/day, but it soon began to decrease in spite of the maintenance of the dose of spironolactone (150 mg/day). This was clearly due to the homeostatic regulation of the body to prevent the aggravation of sodium depletion. Coincident with the decrease in UKV the plasma potassium tended to rise toward the normal level. Thereafter, however, UKV again tended to increase. This rise of UKV was partly due to the

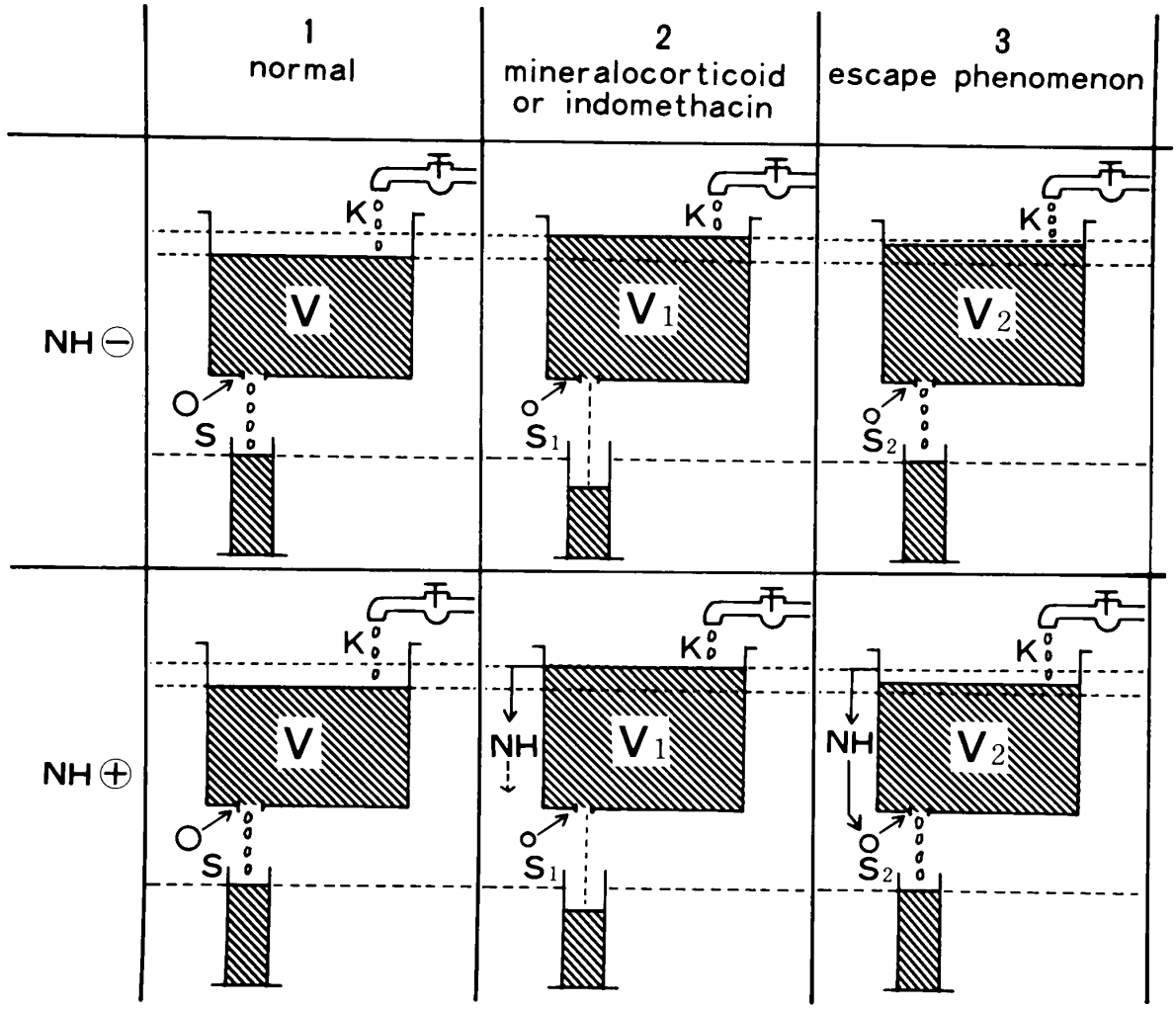

Fig.8. A simple model to explain the regulation of extracellular fluid volume. Extracellular fluid is expressed as isotonic saline filled in a container. Normally the intake of saline is in equibrium with output from the hole at the bottom.
The upper half of the figure shows that the escape phenomenon can be explained only with passive mechanisms. Mineralcorticoid or aspirin-like drugs are assumed to make the hole at the bottom narrower, making an obstruction to the output of the saline in the container. This will cause a transient decrease in the output and thus the elevation of the fluid of level (#2). The elevation of the level will lead to the recovery of the output. This phenomenon (#3) is regarded as an escape. In this way, one could explain the escape. In this way, one could explain the escape phenomenon without consideration of active regulatory facors chaning the resistance to sodium output, namely the size of the hole at the bottom. However, as shown in the lower half, some investigators will want to postulate the participation of a humoral factor other than mineralocorticoid. This factor, usually called a natriuretic hormone, is assumed to be secreted in proportion to the extracellular fluid volume, which is equivalent to the saline volume in the container. Since this factor will cooperate to induce the escape by widening the hole (or decreasing the resistance to the saline output), the escape will occur with less elevation of the fluid level. (See #3 of the lower half in comparison to that of the upper).

increase of aldosterone production as reflected by the increase of PAC, although it is certain that the increase of potassium quantity in the body was a major factor in increasing UKV. (In the case of indomethacin therapy, for example, the retention of potassium eventually led to a kaliuresis under a suppressed PAC level.) At any rate, it seems that the use of spironolactone in order to retain potassium is no good choice because of its induction of negative sodium balance thus stimulating the renin-aldosterone system.

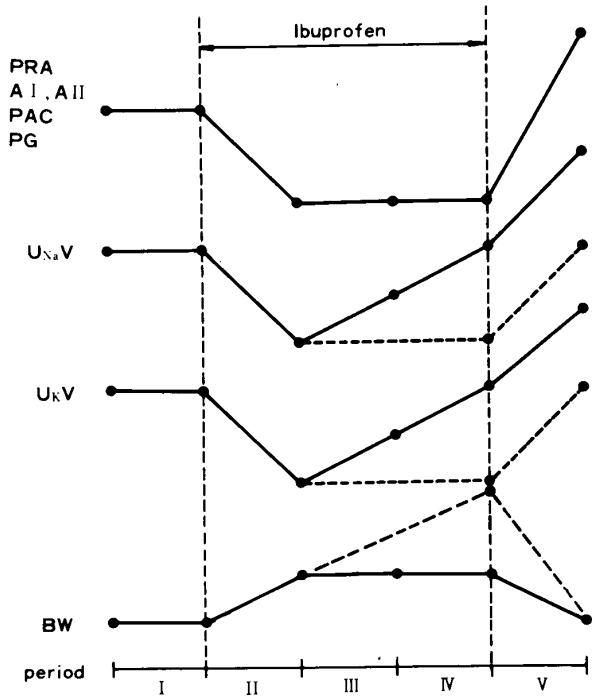

Fig.9. A schematic drawing of the course of ibuprofen therapy to Bartter's syndrome.

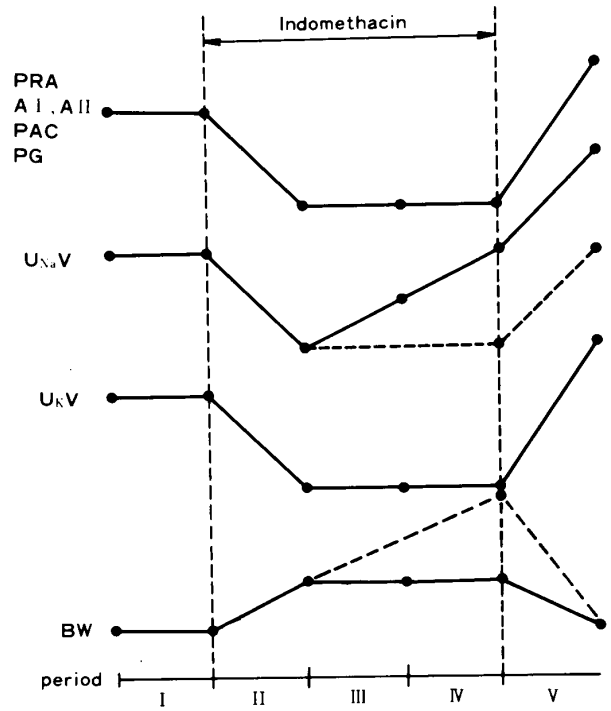

Fig.10. A schematic drawing of the course of indomethacin therapy to Bartter's syndrome.

Response to the Prolonged Treatment with Indomethacin (Figure 7)

The study was continued over eight months. PGE as well as PRA, A I, A II and PAC, which initially fell with the indomethacin therapy,

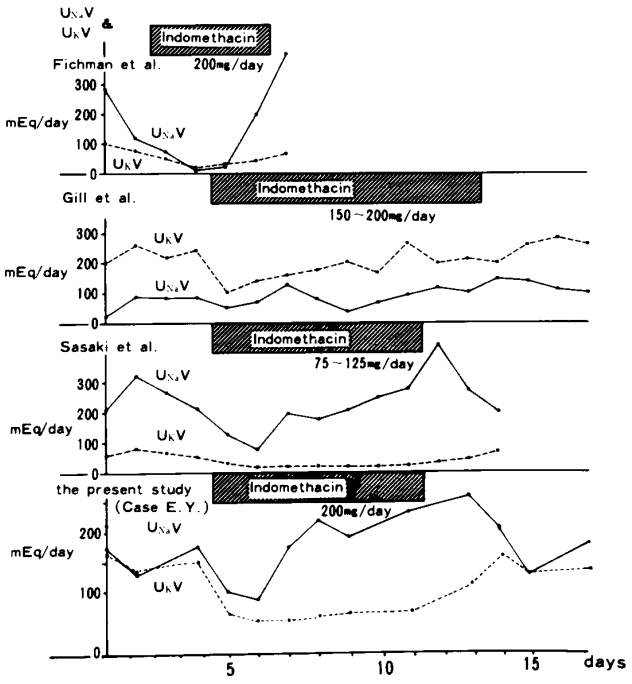

Fig.11. Comparison of the present data with previous ones as to the effects of indomethacin on Bartter's syndrome. In every case an escape is seen to occur on the third day of the indomethacin therapy.

tended to increase gradually in several weeks despite the continued therapy (Figure 7). Plasma potassium was well maintained regardless of the behavior of all hormonal variables under study. When the therapy was transiently stopped at the eleventh week, plasma potassium promptly fell to the initial level. PRA, A I, A II, PAC and PGE also tended to return to their control levels. At the twelfth week, the drug was restarted and was continued for a more prolonged period. During this second trial, all the suppressed hormone levels paradoxically began to rise toward their control values or more in spite of the sustained therapy. Although the plasma potassium also tended to decrease very slightly over this whole period, it also does not appear that the behavior of plasma potassium during the whole process can be explained by the prostaglandin inhibiting effect of indomethacin.

DISCUSSION

Because of findings that urinary prostaglandin E_2 (PGE_2) was high in Bartter's syndrome and that treatment with prostaglandin-synthetase inhibitors corrected the hyperreninemia, the hyperaldosteronism and the vascular hyposensitivity to angiotensin II, an overproduction of

prostaglandins by the kidney has been suggested as a proximal cause of the disorder.[11-16] Nonetheless, prolonged treatment with prostaglandin-synthetase inhibitors fails to correct hypokalemia completely, although normalizing hyperreninemia, aldosteronism and vascular responsivity.[11,12] Furthermore, the specificity of increases in urinary prostaglandin is questioned by the demonstration, in a case report, of reversible prostaglandin E hypersecretion in hypokalemic hypochloremic alkalosis associated with cyclic vomitting.[30] Very recently, evidence was presented for a prostaglandin independent defect in chloride reabsorption in the loop of Henle as a proximal cause of Bartter's syndrome.[31]

In the present study we used plasma levels of PGE, A, and F1α instead of urinary prostaglandins to roughly monitor the effect of prostaglandin inhibitors. Of course there may be a controversy that prostaglandins do not function as circulating hormones, but that they function only as local hormones especially in the kidney. For technical reasons it was not possible for us to measure urinary prostaglandins. However, since it has not been doubted that the aspirin-like drugs universally suppress prostaglandin production in the body it may be allowed to use plasma prostaglandin levels as rough indexes of prostaglandin metabolism. In this respect, it is to be noted that the movement of plasma prostaglandins roughly paralleled those of other hormonal variables, PRA, A I, A II, and PAC.

When one uses aspirin-like drugs for the purpose of inhibiting prostaglandins in the body, the most important thing one should keep in mind may be the escape from their actions of sodium and potassium retention.

Since the escape phenomenon is best known about the mineralocorticoid action, some comments may have to be made about it.[24] It is unlikely that the kidney truely escapes from the effects of the mineralocorticoid action since urinary wastage of potassium persists.[24,25,32] It now seems more likely that, as a result of volume expansion other factors intervene to suppress tubular reabsorption of sodium at an aldosterone independent site or sites in the nephron. This effect then counter-balances and obsures the sodium retaining action of aldosterone.[25,26]

Before comparing the escape phenomena from mineralocorticoid and from aspirin-like drugs, some fundamental considerations should be given to sodium regulations. We made a simplified theoretical model as shown in Figure 8. As can be seen in #1 of upper half of the figure, the body fluid (assumed as isotonic saline for simplicity) is kept in container which has a hole on the bottom. Above the container, there is a faucet to supply the body (container) with the "intake". The "output" from the hole and the "intake" are balanced eventually to maintain the body fluid level. If we assume the constancy of the "intake" (K), the output will be regulated by the size of the hole and by the fluid level (see below). The size of the hole in turn, is regulated by various factors including aldosterone. The fluid level, on the other hand, influences on the output by changing the hydrostatic pressure at the bottom of the container. In other words it could be said that body fluid volume is regulated by two mechanisms. One is active regulation which involves many hormonal and other factors modulating the size of the hole. The other is passive regulation which is governed by the body fluid volume itself. Generally speaking, endocrinologists tend to want to explain homeostasis exclusively by intricately constructed hormonal systems of the body. Such a view is very charming. However, is homeostasis seen only in the higher creatures which have highly evolved hormonal systems? We do not think so.

In the upper half of the Figure 8, the escape phenomenon is explained only due to passive mechanisms. (The regulation due to passive mechanisms is such kind as that the increased body fluid is passively pushed out, thus maintaining the fluid volume as constant as possible. This type of regulation should not need any active, energy-consuming mechanisms. In fact, it is known that when the sodium load is increased the subsequent increase of sodium excretion is closely related to the degree of increase in sodium contents or extracellular fluid volume.[33] If we suppose that mineralocorticoid or aspirin-like drugs make the hole smaller, then the output will be transiently decreased, resulting in the elevation of the fluid level (#2). This elevated level of the fluid will function as a drive force to increase the output until it equals the intake. This last (#3) is the escape phenomenon. Thus one should realize that the escapes can occur without active enlargement of the hole.

As shown in the lower half of the figure, some investigators would postulate the participation of the natriuretic hormone, which is usually thought to be secreted in proportion to extracellular fluid volume,[34] and which conceptually may enlarge the size of the hole (or lessen the resis-

tance against the output). Our mathematical approach using differential equations certified that this introduction of the natriuretic hormone does not change the essence of the escape phenomenon?[7] It only changes the efficiency to keep the volume homeostasis. Namely, the escape can occur with the less elevation of the fluid level. (See #3 of the lower half of Figure 8.)

This theoretical interpretation may seem too idealistic. However, at this stage of medical progress, a simplified model will be needed to give a common basis of discussion in this field. Moreover, the above mentioned passive regulation by means of physical forces is very likely as long as we live under the rule of physical phenomena in this world. As of now, we cannot propose an adequate model of potassium regulations. However, potassium excretion could be governed not only actively by hormonal regulations, but also passively by potassium quantity in the body. (The increase in potassium contents in the body is reflected in plasma levels as well as in intracellular pool of the ion. However, it is known that the accelerated distal tubular potassium secretion seen in the potassium-loaded state is largely due to an increase in the intracellular transport pool of potassium, resulting in a more favorable electrical gradient for secretion?[35,36] Conceptually this should be regarded as a passive mechanism.)

This concept of escape could be made clearer by using Figures 9 & 10. By means of sodium retaining actions of aspirin-like drugs UNaV would theoretically be kept at a certain low level. Assuming a constant sodium intake, the body weight curve would continue rising as indicated by a dotted line. But actually the body fluid escapes or overflows, so to speak, as reflected by the rise of UNaV curve. In the ibuprofen therapy, potassium also begins to escape in concert with this escape of sodium (Figure 9). In the case of idomethacin therapy, however, the escape of potassium delayed in its initiation (Figure 10). Were it not for the escape in this condition, the quantity of potassium in the body would perpetually continue increasing. In fact, this is not the case. The increase in the quantity of potassium would force an overflow of potassium by some passive mechanisms. Since the hormonal variables, including aldosterone, all remained suppressed, they cannot explain the escape of potassium as well as that of sodium.

The course of aspirin therapy went midway between the above two. Judging from this variety of the so-called prostaglandin inhibitors, it is doubtful that these drugs exerted their sodium and potassium retaining actions only through the inhibition of prostaglandin synthesis. Also, it should be stressed now that, if a hormonal factor is truely the mediator of the escape phenomena discussed above, it should be of a completely different nature from the hormonal variables measured in the present studies. For, as long as the factor behaves like the other variables, it necessarily should show a dissociation from UNaV or UKV coincident with the escape phenomena. It is well known that indomethacin has a vasoconstrictor action on renal vessels. Kirschenbaum, Stein and coworkers, however, observed a sodium wasting action of indomethacin in the volume expanded dog, when the vasoconstrictor effects were counteracted by volume expansion?[28,29] The same mechanism may have operated in our patient of Bartter's syndrome when the sodium retention caused by indomethacin reversed the vasoconstrictor effects of that drug itself. Our data, also, suggested that this (sodium) escape phenomenon may have been related to some intrarenal hemodynamic changes.

As a matter of fact, these phenomena are seen not only in the present study but also in previous ones. The data from three other laboratories[11,12,16] are compared with ours in Figure 11. As can be seen, in every case once fallen sodium excretion started to increase towards its control levels on the third day of the indomethacin therapy. Gill et al. apparently became aware of the sodium escape and stated that sodium excretion approached or exceeded that of control values during period 2 (days 5 or 6 through 8 or 9 of indomethacin therapy).[12] In contrast, potassium excretion usually delayed in initiation of the escape (Figure 11). This "delay" is the very thing we interpreted as an inhibition of sodium-potassium exchange in the renal tubules. The shorter the delay, the less effective would be the potassium conserving action. The reason for this variety of the delay period, depending on each study, is not clear.

Interestingly enough, an escape phenomenon occurred with regard to sodium depleting action of spironolactone, as well. This means that the defense mechanism of the body is essentially the same regardless of whether it is concerned with the increase or decrease of the extracellular fluid volume. This phenomenon is just the reverse of the events shown in Fig. 8. The lowered level of the body fluid may well suppress the output

from the hole underneath.

Finally, some comments must be made about the prolonged therapy with indomethacin. Since the patient was not hospitalized during the period of prolonged therapy, the constancy of sodium and potassium intake was somewhat doubtful. This limitation as to an outpatient was probably the main reason for the absence of previous study of prolonged therapy. In our studies, judging from the amount of sodium and potassium in collected urine samples, the intake of these minerals was fairly constant. Moreover, it was apparent that the changes of measured hormonal variables could not be explained by the changes in the intake of sodium or potassium. Fichman et al. and Gill et al. suggested that the failure of indomethacin to totally correct the potassium deficit in their cases may be due to the short duration of therapy.[11,12] According to our experience, there was no evidence that the prostaglandin inhibiting action of indomethacin achieved its complete action over the prolonged period. Rather, PGE tended to revert to or even to surpass control values in a long run. Consequently, the failure to fully correct the hypokalemia cannot be ascribed to the length of duration of therapy. On the contrary, reviewing all the previous data, once elevated plasma potassium tended to fall in several days in most published cases.

The present data paradoxically showed the rise of all plasma hormone levels including PGE toward the end of chronic study. Thus one may possibly suspect that the secondary resistance to prostaglandins could explain the failure of indomethacin to fully correct hypokalemia in previous reports. However, in the present case indomethacin still remained as an effetive antikaliuretic agent even at the end of the chronic study. Thus other factors such as the influence on chloride transport in the loop of Henle may have to be considered in order to explain the effect of this agent.

Acknowledgements

This work was supported by grants from Nippon Miniature Bearing Co., Ltd. and from the Seijinbyo Institute.

REFERENCES

1. CARLSON, L. A., EKLUND, L. G., & ORO, L.: Circulatory and respiratory effects of different doses of prostaglandin E_1 in man. *Acta. Physiol. Scand.* **75**: 161, 1969.
2. WERNING, C., VETTER, W., WEIDMANN, P., & SCHWEIKERT, H. V., et al.: Effect of prostaglandin E_1 on renin in the dog. *Am. J. Physiol.* **220**: 852, 1971.
3. LARSSON, C., WEBER, P., & ANGGARD, E.: Arachidonic acid increases and indomethacin decreases plasma renin activity in the rabbit. *Europe. J. Pharmacol.* **28**: 391, 1974.
4. FROLICH, J. C., HOLLIFIELD, J. W., WILKINSON, G. R., & OATES, J. A.: Effect of indomethacin on furosemide stimualted renin and sodium excretion. *Circ. Res.* **52** (suppl II): 99, 1975.
5. FROLICH, J. C., HOLLIFIELD, J. W., & OATES, J. A.: Effect of indomethacin on isoproterenol induced renin release. *Clin. Res.* **24**: 9A, 1976.
6. MARTINEZ-MALDONADO, M., SAPARAS, N., EKNOYAN, G., & SUKI, W. N.: Renal actions of prostaglandins: comparison with acetylcholine and volume expansion. *Am. J. Physiol.* **222**: 1147, 1972.
7. GROSS, J. B. & BARTTER, F. C.: Effects of prostaglandins E_1, A_1 and $F_2\alpha$ on renal handling of salt and water. *Am. J. physiol.* **225**: 218, 1973.
8. TANNENBAUM, J., SPLAWINSKI, J. A., OATES, J. A., & NIES, A. S.: Enhanced renal prostaglandin production in the dog. 1. Effects on renal function. *Circ. Res.* **36**: 197, 1975.
9. FICHMAN, M. P., LITTENBURG, G., BROOKER, G., & HORTON, R.: Effect of prostaglandin A_1 on renal and adrenal function in man. *Circ. Res.* **31** (Suppl II): 19, 1972.
10. FICHMAN, M., LITTENBURG, G., WOO, J., & HORTON, R.: The effect of prostaglandin PGA_1 on adrenal function in man. *Adv. Biosci.* **9**: 313, 1973.
11. FICHMAN, M. P., TELFER, N., ZIA, P., & SPECKART, P., et al.: Role of Prostaglandins in the pathogenesis of Bartter's syndrome. *Am. J. Med.* **60**: 785, 1976.
12. Gill, J. R., FROHLICH, J. C., BOWDEN, R. E., & TAYLOR, A. A., et al.: Bartter's syndrome: a disorder characterized by high urinary prostaglandins and a dependency of hyperreninemia on prostaglandin synthesis. *Am. J. Med.* **61**: 43, 1976.
13. NORBY, L., LENTZ, R., FLAMENBAUM, W., & RAMWELL, P.: Prostaglandins and aspirin therapy in Batter's syndrome. *Lancet* **2**: 604, 1976.
14. VERBERCKMOES, R., VAN DAMME, B., CLEMENT, J., & AMERY, A., et al.: Bartter's syndrome with hyperplasia of renomedullary cells: successful treatment with indomethacin. *Kidney. Int.* **9**: 302, 1976.
15. DONKER, A. J. M , de JONG, P. E., STATIUS VAN EPS, L. W., & BRENTJENS, J. R. H., et al.: Indomethacin in Batter's syndrome. Does the syndrome represent a state of heperprostaglandinism? *Nephron.* **19**: 200, 1977.
16. SASAKI, H., ASANO, T., OKUMURA, M., & KAWASAKI, T., et al.: The pathogenetic role of renal prostaglandins in Bartter's syndrome *Igaku no Ayumi.* **99**: 863, 1976. (in Japanese)
17. HABER, E., KOERNER, T., PAGE, L. B., & KLIMAN, B., et al.: Application of a radioimmunoassay for angiotensin I to the physiologic measurements of plasma renin activity in normal

human subjects. *J. Clin. Endocr.* **29:** 1349, 1969.
18. GOCHE, D. J., SHERWOOK, L. M., OPPENHOFF, I., & GERTON, J., et al.: Measurement of plasma angiotensin II and correlation with renin activity. *J. Clin. Endocr.* **28:** 1675, 1968.
19. BAYARD, F., BEITINS, I. Z., KOWARSKI, A., & MIGEON, C. L.: Measurement of plasma aldosterone by radioimmunoassay. *J. Endocr.* **31:** 1, 1970.
20. JAFFE, B. M., SMITH, J. W., NEWTON, W. T., & PARKER, C. W.: Radioimmunoassay for prostaglandins. *Science* **171:** 494, 1971.
21. LEVINE, L. & VAN VUNAKIS, H.: Antigenic activity of prostaglandins. *Bioch. and Bioph. Res. Comm.* **41:** 1171, 1970.
22. CALDWELL, B. V., BURNSTEIN, S., BROCK, W. A., & SPEROFF, L.: Radioimmunoassay of the F prostaglandins. *J. Clin. Endocr.* **33:** 171, 1971.
23. HICKLER, R. B.: Prostaglandins symposium of the worcester foundation for experimental biology. Edited by RAMWELL, P. W. & SHAW, J., Interscience, N. Y., 1968, p. 279.
24. AUGUST, J. T., NELSON, D. H., & THORN, G. W.: Response of normal subjects to large amounts of aldosterone. *J. Clin. Invest.* **37:** 1549, 1958.
25. McDONALD, K. M. & SCHRIER, R. W.: Disorders of the renin-angiotension-aldosterone system. In "Renal and Electrolyte Disorders" edited by SCHRIER, R. W., Little Brown and Company, Inc. 1976, p.247.
26. EARLEY, L. E. & DAUGHARTY, T. M.: Sodium metabolism. *New Engl. J. Med.* **281:** 72, 1969.
27. WADA, T.: Role of the third factor in pathogenesis of edema, presented in the "Symposium on Edema: in front of the Japanese Society of Internal Medicine. May, 1978.
28. KIRSCHENBAUM, M. A., WHITE, N., STEIN, J. H., & FERRIS, T.: Redistribution of renal cortical blood flow during inhibition of prostaglandin synthesis. *Am. J. Physiol.* **227:** 801. 1974.
29. KIRSCHENBAUM, M. A. & STEIN, J. H.: The effect of inhibition of prostaglandin synthesis on urinary sodium excretion in the concious dog. *J. Clin. Invest.* **57:** 517, 1976.
30. NIVET, H., GRENIER, B., & ROLLAND, J. C.: Raised urinary prostaglandins in patient without Bartter's syndrome. *Lancet.* **1:** 333, 1978.
31. GILL, J. R. & BARTTER, F. C.: Evidence for a prostaglandin independent defect in chloride reabsorption in the loop of Henle as a proximal cause of Bartter's syndrome. *Am. J. Med.* **65:** 766, 1978.
32. SWINGLE, W. W., MAXWELL, R., BEN, M., BAKER, C., LeBRIE, S. J., & EISLER, M.: A comparative study of aldosterone and other adrenal steroids, in adrenalectomized dogs. *Endocrinology* **55:** 813, 1954.
33. NAGASAKA, M. & KINOUCHI, T.: Symposium on edema; sodium regulatory system and edema *Jap. J. Med.* **67:** 1319, 1979. (in Japanese)
34. SEALEY, J., KIRSHMAN, J., & LARAGH, J.: Natriuretic activity in plasma and urine of salt-loaded man and sheep. *J. Clin. Invest* **48:** 2210, 1969.
35. De MELLO-AIRES, M., GIEBISCH, G., & MALNIC, G.: Kinetics of potassium transport across single tubules of rat kidney. *J. Physiol.* **232:** 47, 1973.
36. WRIGHT, F. S., STRIEDER, N., FOWLER, N. B., & GIEBISCH, G.: Potassium secretion by distal tubule after potassium adaptation. *Am. J. Physiol.* **221:** 473, 1971.