Severe degree of hyperglycaemia: insights from integrative physiology

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Summary

We illustrate how the application of principles of integrative physiology at the bedside can reveal novel insights that have been largely overlooked to this day. In this didactic exercise, modern-day physicians seek an imaginary medical consultation with Professor Sir Hans Krebs because of an unusual finding in his area of expertise: a very severe degree of hyperglycaemia. Although Professor Krebs is restricted to data prior to World War II, this does not prevent him from making novel discoveries. First, he illustrates how an occult factor, rapid absorption of glucose from the intestinal tract, was a critical feature in explaining the basis of the severe degree of hyperglycaemia without obvious ketoacidosis in a 16-year-old patient with type 1 diabetes mellitus in poor control. Second, by examining simple principles of renal and gastrointestinal physiology in a quantitative fashion, Professor Krebs speculates as to how cerebral oedema might occur before therapy in a patient with a severe degree of hyperglycaemia. We hope that readers and educators will appreciate the value of applying principles of integrative physiology in a quantitative fashion at the bedside.

Introduction

For didactic purposes, we selected an imaginary consultant who was a ‘physiological or biochemical giant from the past’, an expert in that area who was called upon to assist our team of modern-day clinicians with an actual case. To illustrate the utility, simplicity, and cost-effectiveness of this approach, we restricted that consultant’s database to medical literature prior to the onset of the Second World War. Despite a total lack of information about molecular biology, or direct experience with problem-based learning or evidence-based medicine, this expert still had at least three advantages. First, he had an in-depth knowledge of the relevant medical literature. Second, he had the confidence to rely on deductive reasoning to propose a hypothesis that he could test with a quantitative analysis. Third, because he was well-versed in integrative physiology, he had an advantage over modern counterparts whose knowledge is much greater in depth, but unfortunately, less developed in breadth.
The physicians seeking the consultation defined the starting point, the very high blood sugar level of 70 mmol/l (1260 mg/dl). Nevertheless, one could just as easily begin with a key finding derived from the history (polyuria), and/or the physical examination (extracellular fluid volume status). Our objective is to illustrate that it is very efficient to begin the clinical analysis with an application of basic principles of integrative physiology. Ultimately, our message to modern clinicians and educators is: ‘Use the principles of integrative physiology at the bedside.’

Section I: issues focusing on diagnosis

Professor Sir Hans Krebs, the discoverer of the Krebs or tricarboxylic acid cycle, is our imaginary consultant. He was asked to explain why the blood sugar was so high in a young female patient with type I diabetes mellitus (DM). The modern attending staff mentioned that this degree of hyperglycaemia was extremely rare in their experience at a pediatric tertiary care hospital.

Before presenting the analysis of Professor Krebs, we invite the reader to stop and answer two questions. First, does the severity of hyperglycaemia imply that the degree of lack of insulin actions is more complete or longer in duration than in patients with more typical values in diabetic ketoacidosis (DKA)? Second, why might this patient have such a severe degree of hyperglycaemia?

1. Does the severity of hyperglycaemia imply that the degree of lack of insulin actions is even more complete than in typical DKA?

Physiology principle 1: When there is a lack of insulin in a young patient with type I DM, two sequelae are expected, ketoacidosis and hyperglycaemia

Return to the bedside: The housestaff were reminded that ketoacids are synthesized normally with sustained insulin lack, so they can serve as a valuable brain fuel during starvation. When ketoacids are added to the body, they dissociate, producing ketoacid anions and H⁺. The H⁺ are buffered primarily with HCO₃⁻ (equation 1). This leads to an increase in the anion gap by an amount equal to the fall in bicarbonate concentration in plasma (Figure 1).

\[
\text{H}^+ + \text{HCO}_3^- \rightleftharpoons \text{H}_2\text{CO}_3^- \rightleftharpoons \text{H}_2\text{O} + \text{CO}_2^- \quad (1)
\]

Therefore Professor Krebs asked for a series of laboratory tests to determine the severity of the ketoacidosis. First, the plasma bicarbonate concentration was 28 mmol/l (normal value 25 mmol/l and there was no vomiting). Second, the plasma anion gap was only very mildly elevated (16 mEq/l). Third, the plasma test for acetone, a metabolic derivative of one of the so-called ketoacids (acetoacetate), was only minimally positive in both the urine and the plasma. This was not typical of diabetic ketoacidosis (DKA) and, at least from the perspective of fat metabolism, was not consistent with a very severe sustained lack of insulin. Thereafter he turned his attention to the degree of hyperglycaemia to see if this might imply a severe lack of insulin.

Physiology principle 2: The plasma glucose concentration is kept within a narrow range

The glucose concentration in plasma must always be high enough to provide a constant supply of fuel to the brain, but never rise enough in normal subjects to cause glucosuria, with loss of fuel, salt and water in the urine. A deficiency of insulin gives ‘metabolic permission’ to have an increased rate of production of glucose and a lower rate of glucose removal by metabolism, thereby leading to an elevated blood sugar level.

Quantitative issues: The size of the glucose pool in the body is very small. The volume of distribution for glucose is close to 50% of total body water (TBW). Hence a 70 kg person will have roughly 75 mmol (13.5 g) of glucose distributed through the extracellular fluid (ECF) compartment and in organs such as the liver where insulin is not required for glucose transport into its intracellular fluid (ICF) compartment (5 mmol/l x 15 l). This pool size of 75 mmol is close to 5% of the daily throughput (intake and disposal) of approximately 270 g (1500 mmol) of glucose. Given these numbers, a mismatch between intake and output could easily cause large changes in plasma glucose levels, especially if the ability to remove glucose by metabolism was compromised.

Return to the bedside: Professor Krebs took great delight in adding a few succinct insights about the metabolism of glucose. With insulin deficiency, removal of glucose by oxidation is low, because fat-derived fuels are being oxidized. Later studies demonstrated that the products of the oxidation of fatty acids inhibit glucose utilization in organs such as skeletal muscle by inhibiting the enzyme pyruvate dehydrogenase.

In addition, even the brain could not continue to use glucose at its usual rate of about 28 mmol/h
(5 g/h) if ketoacids were present and being oxidized in this organ. Moreover, there is very little synthesis of glycogen in an insulin-deficient state. Professor Krebs concluded by saying that, while insulin lack is a vital permissive element, factors affecting input into and output from a small body glucose pool were more important in generating extremely high blood sugar levels. Therefore, he turned his attention to Question 2.

2. Why might this patient have such a severe degree of hyperglycaemia?

Professor Krebs did not trust anecdotal comments, and asked if one of the physicians would verify that a blood sugar value that exceeded 60 mmol/l (1080 mg/dl) is indeed rare in young patients admitted with diabetes mellitus in poor control. He suggested that all the hospital charts in this patient group over the past several years be examined for blood sugar levels. While awaiting the results, Professor Krebs turned his attention back to the patient. His first step was to determine why the blood sugar was so high. For this deduction, he relied heavily on the third physiological principle.

**Physiology principle 3:** To have a higher concentration of a metabolite such as glucose in plasma, glucose input should be higher than glucose output by a quantitatively appropriate amount (Figure 2)

*Return to the bedside:* Professor Krebs stated that the first step was simply to obtain data on output by measuring the rate of excretion of glucose. Therefore, he wished to know what the urine flow rate was before therapy was initiated. He fully expected to find little excretion of glucose because of a major reduction in glomerular filtration rate (GFR), the consequence of a deficit of sodium (Na⁺) due to the prior osmotic diuresis. He was, therefore, taken aback to find a urine flow rate of close to 10 ml/min (equivalent to approximately 15 l/day) along with a near-normal GFR as reflected by the values for the concentration of creatinine (88 μmol/l, 1.0 mg/dl) and urea (8 mmol/l, BUN 21 mg/dl) in plasma. Moreover, he knew that it would be very difficult indeed to sustain a very high input of glucose, even though it is common for these patients to consume a large volume of glucose in sweetened beverages. At this point the housestaff recognized the importance of the polyuria and asked, ‘How fast might glucose be excreted in this patient?’

![Figure 1. Ketoacid metabolism.](https://academic.oup.com/qjmed/article-abstract/95/2/113/1528650/115)
3. How fast might glucose be excreted in this patient?

To answer this question, Professor Krebs reviewed the physiology of glucose handling by the kidney.

**Physiology principle 4: The renal excretion of glucose occurs once the glycaemic threshold of around 10 mmol/l (180 mg/dl) is exceeded.**

Return to the bedside: Glucosuria has the largest capacity to remove glucose in this patient (Table 1). The professor knew from his reading that 50–60 g or close to 300 mmol of glucose are typically excreted per litre of urine during a glucose-induced osmotic diuresis.1 This quantity of glucose is equal to the amount of glucose in half a litre of apple juice.

At this point, there was a phone call from an interested laboratory technician. She reported that the results from the second blood sample drawn 100 min after admission were available. To everyone’s surprise, despite the fact that the urine output over this 100 min interval was 1 l, there was no change in glycaemia (70 mmol/l) despite an estimated urinary loss of 300–400 mmol of glucose. With these data in hand, the professor expanded on his quantitative analysis. Her GFR was likely to be 6 l over our 100-min time interval. With a plasma glucose level of 70 mmol/l for this entire 100 min, the kidney could excrete 300–400 mmol of glucose [6 l × 60 mmol/l (70 mmol/l minus the renal threshold of 10 mmol/l)]. These numbers highlight the large renal capacity to eliminate glucose when the GFR is maintained (Table 1). Excessive input, he proclaimed, must be the major culprit to explain the unusual degree of hyperglycaemia in view of the very high renal elimination of glucose. While glucose entry into the body pool can be from endogenous or exogenous sources, he had dismissed the former as a serious possibility with an elegant quantitative analysis (Appendix 1). Professor Krebs was sure that our team of physicians would agree that exogenous glucose and not endogenous production was the cause of hyperglycaemia and shifted his focus to events in the gastrointestinal (GI) tract.

Professor Krebs was about to continue his analysis of input when he was interrupted by the report of the chart review of usual admission blood sugar levels in young patients with diabetic ketoacidosis. A review of all the patient charts with the diagnosis of severe hyperglycaemia or DKA over the past two years had confirmed the impression that this degree of hyperglycaemia is distinctly unusual (Figure 3). The ever-alert Senior Resident, however, stopped our illustrious consultant in his tracks when he posed the following excellent question, ‘Why do most diabetics and even normal subjects not develop severe hyperglycaemia when they ingest large amounts of glucose?’

4. Why does a high intake of glucose seldom cause hyperglycaemia?

At this juncture, Professor Krebs gave them perhaps the most valuable lesson of all. He announced that his grasp of the physiology of glucose absorption in the GI tract was incomplete and proceeded to consult with a colleague, the eminent GI physiologist, Horace Davenport. From this interaction was born the fifth physiological principle which is expanded upon below.

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Table 1 Effect of hyperglycaemia and glomerular filtration rate on excretion of glucose

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<tr>
<th>Plasma glucose (mmol/l)</th>
<th>GFR (l/100 min)</th>
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Data show glucose excreted (mmol/100 min). Excretion of glucose (mmol/100 min) = (GFR (l/100 min) × (plasma glucose−10 mmol/l)) (the renal glucose reabsorbed/litre GFR). Note the very high levels of glucosuria when there is both hyperglycaemia (70 mmol/l) and a modestly reduced GFR (6 l/100 min) (value in bold). For comparison, a normal diet will supply an average of 18 g or 100 mmol of glucose per 100 min.
Physiology principle 5: Control of stomach emptying is a powerful mechanism to protect against hyperglycaemia

Return to bedside: The magnitude of the glucose load and the speed with which it is added to the body is a ‘clinically occult’ yet major factor that might determine the degree of hyperglycaemia when there is a deficit of insulin actions at any point in time. For this glucose entry, one needs both the ingestion of glucose-containing fluids and delivery of this solution to the absorptive surface of the intestinal tract. Careful questioning of the patient elicited a history of marked thirst and the intake of large amounts of water and apple juice (glucose concentration close to 750 mmol/l) in the hours preceding admission (Appendix 2 for case summary). This history is common in patients with DKA, yet this severe degree of hyperglycaemia is rare (Figure 3).

While in the emergency department, the patient continued to drink, but the intake was now just water. Professor Davenport advanced the hypothesis that their patient may have accumulated a large quantity of glucose (apple juice) in her stomach or in the lumen of the intestinal tract if the latter were dilated due to slow motility. He wondered whether this patient could have had a stimulus causing accelerated gastric emptying and/or GI motility that led to rapid glucose absorption from the GI tract shortly before she was admitted to hospital (see Appendix 3). He issued a caution—the composition of the fluid in the stomach would undergo a change because of this ongoing intake of water without sugar.

The next step was to plan therapy based on the new insights they had gained. Professor Krebs then asked the physicians on rounds, ‘In what way might this degree of hyperglycaemia “help” our patient?’ We invite the reader to pause and answer this question.

5. In what way might this degree of hyperglycaemia ‘help’ our patient?

The housestaff were taken off-guard by this question. It was their impression that such a high blood sugar value was obviously detrimental, although admittedly, they were relying on clinical impressions and statistical associations rather than having a pathophysiologic basis for their view.

Our professor urged them on by asking ‘Where would virtually all this extra glucose be in the body of our insulin-deficient patient?’ They responded correctly, saying that most of the glucose would be in the ECF compartment (with a smaller quantity of glucose in hepatocytes, erythrocytes and kidney cells because these organs did not need insulin to augment glucose transport).

Now Professor Krebs added his coup de grace, a quantitative analysis. For simplicity, he said, assume her ECF volume is normally 10 l, because she weighs 50 kg and her ECF volume is 20% of body weight. He thanked the house officer who told him that there was no evidence of a major decline in her ECF volume on physical examination on admission. Therefore, he continued, she had an extra 650 or so mmol of glucose in her ECF compartment ((70–5 mmol/l)×10 l). With a plasma effective osmolality of close to 300 mOsm/l, this degree of hyperglycaemia would be responsible for maintaining 2 l or 20% of her current ECF volume and thereby probably helped her maintain an adequate circulatory hemodynamic status.

Summary: Before defining his plan for therapy, Professor Krebs summarized the major features in this case. From his metabolic analysis, he concluded that the patient was clearly suffering from a deficiency of insulin that was sufficient to permit hyperglycaemia, but not severe or prolonged enough to cause a clinically important degree of ketoacidosis. The most decisive findings were the combination of a very severe degree of hyperglycaemia and a large glucose-induced osmotic diuresis. That the required input of glucose was so big meant that it had to arise from an exogenous source. He also emphasized that this degree of polyuria required that the effective blood volume be
close to normal (i.e. a near-normal GFR). This in turn was due in part to the glucose and water retained in the body, re-expanding the ECF volume. He further cautioned that this severe degree of hyperglycaemia would resolve when the input of glucose decreased, but that the rate of stomach emptying as well as the concentration of glucose in the fluid retained in the stomach were important yet unknown variables.

Section II: issues for therapy

The critical issues for therapy over the next short while would be related to defence of the ECF volume and to factors that might lead to brain swelling. Given this focus, Professor Krebs asked the following question. In what way is the composition of the ECF compartment currently abnormal? We again ask the readers to provide their own answer to this question.

1. In what way is the composition of the ECF compartment currently abnormal?

Physiology principle 6: The volume of the ECF compartment is dependent on two factors, the number of osmoles restricted in distribution to the ECF compartment and the overall concentration of these particles

The ECF volume is determined by the number of effective osmoles in her ECF compartment divided by the effective osmolality or tonicity of the ECF compartment. Professor Krebs might have called these osmoles tonomoles to emphasize how they differed from compounds such as urea that cross the ECF:ICF interface, have an equal concentration in both of these compartments, and do not influence compartment volumes. In this patient, the tonomoles in the ECF compartment are Na\(^+\) plus its attendant anions as well as glucose.

Return to the bedside: Professor Krebs had already been told that the clinical impression was that the ECF volume was close to its normal value of 10 litres. Assuming this to be true for the moment, he needed to know one other fact, the plasma Na\(^+\) concentration. He was told that this was 123 mmol/l. Therefore he deduced that the total content of Na\(^+\) in her ECF compartment was reduced by 170 mmol [10 litres×(140–123 mmol/l)] (Figure 4). Because the content of glucose in her ECF compartment was increased by close to 650 mmol (70–5 mmol/l×10 l), there was a rise in the content of tonomoles (deficit of 2×170 or 340 mOsm of electrolytes and a gain of 650 mOsm of glucose). This rise in tonicity would obligate the movement of close to 2 l of water (10% of the ICF volume of 20 l) to the ECF compartment and ultimately to the urine in this patient. Professor Krebs recognized, but for the moment chose to ignore this water shift for simplicity.

Professor Krebs then threw down the gauntlet and asked: ‘What should the therapy be for the excretion of one litre of urine during the initial brisk osmotic diuresis?’ He reminded them that its likely composition was 350 mmol of glucose and 50 mmol of Na\(^+\) per litre. Should we replace this urinary loss with isotonic saline, hypotonic saline, hypertonic solution, or should we not replace it at all?’

2. What should the therapy be for the excretion of 1 l by osmotic diuresis?

There was a stunned silence around the bedside. A rationale could be provided for each option, but which one was correct? In the first 100 min since admission, they had given the patient 1 l of isotonic saline to match the urine output of 1 l. They had assumed that this would result in neutral water balance (1 l in, 1 l out) and the replacement of close to 300 mmol of glucose lost in the urine by 300 mmol of electrolytes as isotonic saline. The plasma glucose was expected to fall by 20 mmol/l (300 mmol lost/15 l volume of distribution). After their initial hesitation, our physicians broke out into animated discussion. We again ask the reader to pause and make their own decision before moving to the next paragraph.

Return to the bedside: Everyone realized that a rapid decrease of ECF volume could lead to hypoperfusion and that this should be avoided. Moreover, glucose was ‘protecting’ the ECF volume in this patient by causing the retention of 2 l of water in this compartment. It was clear to them that 1 l of output might represent the loss of 1 l of ECF volume and that the litre of isotonic fluid that they gave should maintain the normal ECF volume.

Suddenly, one resident recognized that the input from the GI tract had to be taken into account before a proper decision could be reached about the choice of fluid to be administered. For example, as long as there was absorption of fluid from the GI tract with a composition that matched urine output (in terms of volume and number of tonomoles), the ECF volume would be maintained without giving an infusion of saline (Figure 5, left panel). In fact, if saline were administered in this setting, it would expand her ECF volume. The challenge then was to replace only those ECF losses that were not being replaced by entry from the GI tract. Nevertheless, there was no direct way to monitor stomach contents or the rate of stomach emptying.
A bright young medical student came up with a simple answer that amazed his colleagues and brought a big smile to the friendly face of Professor Krebs. This student had grasped physiological principle 3 and presented it in a modified form. 

Physiology principle 3 restated: When a parameter such as the blood glucose concentration remains constant over a period of time, input must equal output for that period if there is no change in the ECF volume

Return to the bedside: Applying this principle to the case, our young colleague knew that observing the fall (or lack of it) in plasma glucose concentration would tell them whether the supply of glucose from stomach absorption was matching the rate of glucose loss in the urine. This principle was utilized to examine events in the first 100 min after admission (Figure 5). In that period, there was no appreciable change in the plasma glucose or Na⁺ concentrations, implying that glucose disposal by osmotic diuresis was being matched by glucose and water entry from the GI tract. Therefore intravenous saline was not needed to avoid a change in the ECF compartment volume and composition (to be absolutely correct, 50 mmol of NaCl should have been given).

The smile broadened on the face of their beloved professor. In the next 120 min, there were to be dramatic differences in plasma composition. One litre of urine was also excreted, but there was a drop in glycaemia of 30 mmol/l. This provided
clear evidence that glucose absorption from the GI tract had slowed markedly. In quantitative terms, the glucose content in the ECF compartment had decreased by close to 300 mmol, an amount easily excreted by the kidney and representing 11 of ‘glucose-containing ECF’. Replacement of ECF volume with 11 of isotonic saline would prevent any haemodynamic insult. Professor Krebs then asked, ‘What changes should this cause in the plasma Na$^+$ concentration?’

3. What are the expected changes in plasma Na$^+$ concentration?

The housestaff were brimming with confidence, having ‘absorbed’ the fruits of the teaching surrounding this case. They performed their own quantitative analysis. They stated that one litre of intravenous fluid was given and 11 of urine was excreted so there was water balance. As the intravenous infusion was isotonic saline, 150 mmol of Na$^+$ had been infused. Because the urinary Na$^+$ concentration was 50 mmol/l, there was a positive balance of 100 mmol of Na$^+$. The smile was still evident on Professor Krebs’ face, so they continued. A positive balance of 100 mmol of Na$^+$ should raise the ECF osmolality and draw water out of the ICF compartment. Accordingly, they said, this Na$^+$ gain was behaving as if it was ‘dissolved’ in total body water (30 l for simplicity) and therefore the plasma Na$^+$ concentration should rise by 3.3 mmol/l (100 mmol in 30 l).

The look of disappointment on the countenance of their admired instructor, however, indicated that they had made a major error in logic. How did Professor Krebs know that they had erred in their analysis?

4. How did Professor Krebs know that they had erred in their analysis?

Physiology principle 6 restated: The volume of the ECF compartment is maintained by the number of tonomoles in that location. The content of tonomoles is revealed by mass balance (physiological principle 3)

Return to the bedside: On mass balance, the ECF compartment had lost 300 mmol of glucose while retaining 150 mmol of Na$^+$ and 150 mmol of Cl$^-$(Figure 5). Therefore, the total number of tonomoles in the ECF compartment was largely unchanged, so there should be no shift of water across the ECF:ICF interface. Accordingly, the expected rise in natraemia should be 10 mmol/l (100 mmol in 10 l of ECF). The modern medical student, although impressed with this logic, stated that he had read a number of papers suggesting a relationship between changes in glucose concentration and the plasma Na$^+$ concentration (references 5 and 6 were not available to Professor Krebs). Professor Krebs patiently pointed out that these calculations were based on adding hypertonic glucose to the body, a situation different from that of our patient. He stated firmly, ‘Never apply data from one set of conditions to a second setting where the conditions are not identical’.

From the above discussion, the goals of therapy became obvious (Figure 5). Nevertheless, because the plasma tonicity (glucose and Na$^+$ concentrations) would only be known in retrospect, the initial intravenous fluid therapy was isotonic saline at a rate equal to the urine volume for the first 100 min. Therapy will then be dictated by the changes in the plasma glucose concentration and the physical examination. One should replace the urine volume with isotonic saline only if there is a suitable fall in glycaemia. The expected values are that the rise in natraemia should be close to half the decline in glycaemia to maintain a constant plasma tonicity and thereby avoid inducing ICF volume expansion and as a result, brain cell swelling.

A new wave of confidence was present. All were certain that the plasma Na$^+$ concentration would have risen from 123 mmol/l to the mid-130 range. A surprise was in store—the plasma Na$^+$ concentration was virtually unchanged at 122 mmol/l. Professor Krebs was not shaken, but he had a look of concern on his face. Again he asked for an explanation from his enthusiastic pupils.

**Physiology principle 6 restated:** The concentration of Na$^+$ in plasma will decline if either this tonomole is lost from the ECF compartment in hypertonic form and/or if there is an addition of water to the ECF compartment

**Return to the bedside:** The only way to lose hypertonic saline is via the urine, but this did not occur in our patient. Water can be added to the ECF compartment as an isotonic but Na$^+$-poor solution or as a hypotonic fluid (Figure 6). Because the tonicity of plasma fell while there was an apparent total tonomole balance, it is likely that there was an addition of hypotonic fluid. Since the intravenous fluid was isotonic saline, the source of the hypotonic input was likely to be from the GI tract. At this point, the admitting physician reminded everyone that the patient had continued drinking large volumes of water instead of fruit juice since coming to the hospital.
As understanding dawned, there was also a look of concern on the faces of the physicians taking care of this patient. Please consider ‘What is the current threat to this patient?’

5. What is the current threat to this patient?

Physiology principle 6 restated: The volume of the ICF compartment will rise when the tonicity of the ECF compartment declines and if the number of tonomoles in the ICF compartment remains constant.

Return to the bedside: Because the new calculated tonicity of plasma had fallen from 316 to 284 mOsm/kg H2O (2×122 mmol Na+/l + 40 mmol glucose/l), there would be an expansion of the ICF volume. Brain cell swelling was an obvious new threat to the patient if glucose had entered the brain when the plasma tonicity was 316 mOsm/kg H2O. Because brain cells occupy close to 80% of the volume within the bony skull, a rise in intracranial pressure could be anticipated. Death might result from herniation of the brain through the foramen magnum. Accordingly, the attending physicians thought it advisable to give this patient hypertonic tonomoles. They decided that 960 mOsm [(316–284 mOsm/kg H2O)×30 l of body water] of hypertonic saline would be required to raise the body tonicity to its prior value, and that this should be done relatively quickly.

The housestaff then thanked Professor Krebs for an outstanding teaching session. He acknowledged their appreciation with his characteristic humility, but pointed out that there was still one unanswered question. ‘Why would the administration of hypertonic saline lower the intracranial pressure?’

6. Why would hypertonic saline lower intracranial pressure?

Our housestaff were now able to avoid obvious pitfalls. They reasoned that to lower intracranial pressure, they would have to draw water out of the skull, not just out of brain cells (Figure 7).

Therefore, the tonomole added must remain within the vascular space and not enter the brain ECF compartment. On hearing this, Professor Krebs beamed with satisfaction, enjoying the rewards due to a truly gifted teacher.

Concluding remarks

The analysis of this unusual case illustrates our approach to problem-solving in the area of glucose and energy metabolism. This way of thinking is based on integrative physiology and has also served us well when applied to fluid, electrolyte and acid-base disorders. In short, we identify a key abnormality, then analyse it using the appropriate physiologic principles, at all times including a quantitative approach. A summary of the principles applied to this case is provided in Table 2.

In this paper, we highlighted two ideas whose importance have previously not been fully appreciated. First, while the need to consider input is obvious when looking at external balance, most of our attention has been focused on output. We have detailed knowledge of how a substance may be
disposed of by metabolism or renal excretion, but our understanding of factors governing input from the GI tract is far less well-developed. Our case, an example of the diabetic hyperglycaemic hyperosmolar syndrome due to high glucose intake and absorption from the GI tract, brings home the importance of a better understanding of ‘input physiology’. It appeared to explain the very severe degree of hyperglycaemia. Moreover, while the numbers were consistent with a steady state of hyperglycaemia for 100 min, the magnitude of glucosuria implied that it is extremely unlikely that this would represent a steady state over 24 h. This aspect of variability of the rate of stomach emptying and composition of stomach contents in a patient with DM in poor control will no doubt be a fertile area for further investigation. Second, it is well known that cerebral oedema (really brain cell swelling) may develop in poorly controlled diabetics even before therapy is commenced. Going back to basic principles of physiology means evaluating the elements involved in water movement across cell membranes, namely water permeability and the driving force, a temporary difference in effective osmolality between the ICF and ECF compartments. In this case, the fall in effective osmolality occurred initially in the ECF compartment and was manifested by a sharp drop in plasma glucose concentration and not, as is more commonly seen, an acute fall in the plasma Na⁺ concentration. The basis for this sharp drop in effective osmolality in a patient given isotonic saline was clinically occult, in that the hypotonic water load was obtained by absorption of water from the GI tract. A shift in focus to the more relevant parameter, plasma effective osmolality, is therefore required instead of simply considering the plasma Na⁺ concentration.

In conclusion, we hope that the reader might be persuaded to consider this method of analysis and support our contention that a diagnostic and therapeutic strategy based on principles of integrative physiology is as relevant today as it ever was.

**Appendix**

1. **Endogenous production of glucose**

   Of the 500 g of glycogen in the body, 80% is in skeletal muscle and most of this pool cannot be converted directly to body glucose. For this conversion, L-lactate must be released into the plasma. Nevertheless, the plasma level of L-lactate did not become elevated (recall the near-normal values for the plasma bicarbonate and anion gap). Only the 100 g (550 mmol) of glycogen stored in the liver could be utilized and this is a one-time-only addition to the glucose pool. Professor Krebs doubted that protein breakdown and gluconeogenesis could be quantitatively important sources of glucose, because of the relatively low appearance of urea (plasma urea was 8 mmol/l and GFR was estimated at 6 l/100 min). Therefore close to 50 mmol of urea were excreted in this 100 min, and with no change in the plasma urea concentration, the urea appearance rate was close to 50 mmol. During conversion of protein to glucose, close to 2 mmol of urea are synthesized per mmol of glucose formed. Thus the excretion of only

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**Table 2** Summary of physiological principles

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<td>1. [Glucose] in plasma is tightly defended</td>
<td>Too low is a problem for the brain</td>
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<tr>
<td>2. Lack of insulin actions should lead to hyperglycemia and ketoadiposis</td>
<td>Hyperglycaemia reflects loss of insulin. Degree depends on other factors (renal, GI)</td>
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<td>3. A high concentration of glucose = high input and/or low output</td>
<td>High input of glucose will cause polyuria</td>
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<td>4. Very high input of glucose requires an exogenous source</td>
<td>Need high intake of glucose (e.g. fruit juice)</td>
</tr>
<tr>
<td>5. ECF volume is determined by number of effective osmoles</td>
<td>Usual effective osmoles are Na⁺ + anions</td>
</tr>
<tr>
<td>6. Hyponatremia usually means ICF volume expansion</td>
<td>May be due to Na⁺ loss from ECF</td>
</tr>
<tr>
<td>7. To know ICF volume, examine effective osmolality</td>
<td>Plasma [Na⁺]×2 plus glucose in mmol/l terms</td>
</tr>
</tbody>
</table>

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50 mmol urea excluded true gluconeogenesis as a quantitatively important source of glucose.

2. Case summary

A 16-year-old female with type I DM had not been diligent about achieving good glycaemic control. She had had four previous admissions for DKA. She had not taken insulin injections for 2 days prior to arrival in hospital despite recording a blood sugar level of 27 mmol/l. The reason for the present admission was exceedingly troubling polyuria and polydipsia; her major fluid intake while outside of hospital was fruit juice. She admitted taking street drugs, but did not reveal their nature. The physical examination did not reveal any major abnormalities. Of note, her blood pressure was 105/66 mm Hg and her pulse rate was 80/min. The most striking laboratory feature was an unusually high blood sugar value of 70 mmol/l. Of particular importance, her blood pH was 7.33 and her bicarbonate concentration was 28 mmol/l. The plasma anion gap was 16 mEq/l. Plasma sodium concentration was 123 mmol/l and her plasma potassium concentration was 4.8 mmol/l.

3. Control of gastric emptying

Normal individuals are very effectively protected against hyperglycaemia by having a slow and tightly regulated rate of gastric emptying when the blood sugar rises. There appear to be two major types of signals that contribute to this regulation. The first type of signal is via chemical mediators. An example of one signal system is amylin that is released from the islets of Langerhans in response to an elevated glucose level in the arterial blood. The other chemical mediators are of intestinal origin and their release is triggered by a local glucose load. Glucagon-like peptides (GLP) are probably important in this regard. Both amylin and GLP also suppress appetite. The second set of signals is triggered by mechanical forces. When the duodenum is distended, gastric emptying is delayed. In all of these setting, the gastric cholinergic system and serotonin receptors seem to play a role. All of these control systems seem to act in concert to decrease the rate of entry of glucose into the circulation to match its rate of removal by metabolism while not raising the plasma glucose concentration above the renal threshold (Figure 8). This whole system seems to limit caloric entry to 200 kcal/h.

In patients with DM, hyperglycaemia should slow gastric emptying, even in the absence of autonomic neuropathy. Conversely, when the pyloric sphincter relaxes, as seemed to occur in our patient, stomach emptying may be rapid, resulting in a severe degree of hyperglycaemia and a marked degree of polyuria if the GFR is not low (Table 1).

References


