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MEDICAL GRAND ROUNDS

PARKLAND MEMORIAL HOSPITAL

November 6, 1969

A CELLULAR DEFECT IN SEVERE ILLNESS

Mild Illness

CASE 1 - [redacted]

This 27 year old [redacted] female had received Tripac and Streptomycin therapy for tuberculous meningitis and probable pulmonary tuberculosis. At the time of muscle study she had had several weeks of therapy and was essentially well except for slight ataxia and low-grade fever.

Muscle Transmembrane Potential	-87 mV
Serum $[K^+]$	3.9 mEq/L
Muscle $[K]$	146 mEq/L
Muscle $[Na]$	19.8 mEq/L
Predicted Em (Goldman)	-88 mV

Severe Illness

CASE 2 - [redacted]

This 39 year old [redacted] female, known alcoholic, had a 10 year history of chronic recurrent pancreatitis. The present admission was for hematemesis which resulted in a partial gastrectomy and the finding of a benign ulcer and a pancreatic pseudocyst.

Muscle study was done post-operatively.

Muscle Transmembrane Potential	-74 mV
Serum $[K^+]$	4.0 mEq/L
Muscle $[K]$	130 mEq/L
Muscle $[Na]$	41.0 mEq/L
Predicted Em (Goldman)	-85 mV
Calculated pNa	0.06

CASE 3 - [redacted]

This patient, a 45 year old [redacted] female, had a 5 year history of scleroderma. She was in a down-hill phase of her illness when the muscle studies were done having pulmonary and cardiovascular problems.

Muscle Transmembrane Potential	-67 mV
Serum [K+]	4.1 mEq/L
Muscle [K]	182 mEq/L
Muscle [Na]	29.9 mEq/L
Predicted Em (Goldman)	-91 mV
Calculated pNa	0.06

Uremia

CASE 4 - [redacted]

This 59 year old [redacted] female had a long history of hypertension, congestive heart failure and progressive decrease in renal function. At the time of the muscle study, she had minor uremic symptoms. Had last previous peritoneal dialysis about 3 weeks previously.

Muscle Transmembrane Potential -54 mV

BUN	53 mg%
Creat	8.2 mg%
Na	129 mEq/L
K	3.6 mEq/L
Cl	102 mEq/L
CO_2	16 mM/L
pH	7.36

CASE 5 - [redacted]

A 28 year old [redacted] male with end-stage renal disease being carried with conservative therapy and intermittent dialysis.

Muscle study done in clinic during routine visit. Patient was having significant symptoms at the time.

Muscle Transmembrane Potential -67 mV

BUN	150 mg%	Muscle [K]	140 mEq/L
Creat	20.7 mg%	Muscle [Na]	25 mEq/L
Na	136 mEq/L		
K	4.5 mEq/L	Predicted Em (Goldman)	-84 mV
Cl	95 mEq/L		
CO_2	15 mM/L	Calculated pNa	0.05
pH	7.33		
RBC [K]	99.7 mEq/L		
RBC [Na]	6.31 mEq/L		

CASE 6 - [redacted]

A 57 year old [redacted] male being followed in Renal Clinic for conservative therapy of near end-stage renal disease due to chronic glomerulonephritis.

Muscle Transmembrane Potential -70 mV

BUN	145 mg%	Muscle [K]	128 mEq/L
Creat	24 mg%	Muscle [Na]	27.8 mEq/L
Na	136 mEq/L		
K	3.6 mEq/L	Predicted Em (Goldman)	-86 mV
Cl	103 mEq/L		
CO_2	14.4 mM/L	Calculated pNa	0.04
pH	7.23		
RBC [K]	101 mEq/L		
RBC [Na]	7.96 mEq/L		

CASE 7 - [redacted]

A 33 year old [redacted] male undergoing chronic hemodialysis for therapy of end-stage renal disease.

Muscle Transmembrane Potentials measured pre- and post-dialysis.

	Pre-dialysis	Post-dialysis
Em	-62 mV	-88 mV
BUN	75 mg%	22 mg%
Creat	11.7 mg%	4.5 mg%
Na	134 mEq/L	138 mEq/L
K	4.9 mEq/L	4.0 mEq/L
Cl	96 mEq/L	97 mEq/L
CO_2	19 mM/L	24 mM/L
pH	7.36	7.45

Muscle [K]		132 mEq/L
Muscle [Na]		18.5 mEq/L
Predicted Em (Goldman)		-83 mV
RBC [K]	103 mEq/L	102 mEq/L
RBC [Na]	9.36 mEq/L	10.12 mEq/L

Hypokalemia

CASE 8 [redacted]

A 33 year old [redacted] female who began her illness 20 years PTA with difficulty swallowing. There had been a slow progression of her illness characterized by weakness in the face, neck and shoulder girdle. She had had frequent pulmonary infections.

There was evidence for both a primary muscle disease and a polyneuropathy.

At the time of study her serum $[K^+]$ was 3.3 mEq/L. Muscle Transmembrane Potential was -53 mV.

Muscle [K] 138 mEq/L
Muscle [Na] 45.5 mEq/L

Predicted Membrane Potential (Goldman) -91 mV

Calculated pNa 0.06

CASE 9 [redacted]

Apparently as the result of poor dietary intake and vomiting, this 25 year old Negro female was admitted with severe hypokalemia. She was in the last trimester (some 60 days from EDC) of her ninth pregnancy. She was markedly weak at the time of admission and shortly following admission her extremities became totally paralyzed. Her serum $[K^+]$ was 1.3 mEq/L.

After a small amount of KCl, she regained the use of her extremities, but was still weak. Her serum $[K^+]$ = 2.2 mEq/L. Muscle Transmembrane Potential at that time was -65 mV.

Following five days of normal diet supplemented with about 1500 mEq KCl she appeared normal and her serum $[K^+]$ was 4.1 mEq/L. Muscle Transmembrane Potential at that time was -81 mV.

Interestingly, she returned one month later, again hypokalemic and delivered a premature infant that died.

CASE 10 [redacted]

This 24 year old [redacted] female was admitted to the hospital, in the last month of what had apparently been an uncomplicated pregnancy, because of extreme weakness. On admission, her weakness was so profound that she could not move her extremities. She was found to be hypokalemic (Serum $[K^+]$ = 1.8 mEq/L) with marked ECG changes. She had apparently lost potassium by means of vomiting. Some parenteral KCl was administered and her serum $[K^+]$ rose to 2.5 mEq/L. At this point muscle studies were done.

Serum CPK	573u	Serum $[K^+]$	2.5
Serum Aldolase	19.5_u	Serum $[Na^+]$	139
Muscle Transmembrane Potential			-63 mV
Muscle Composition		$[K^+]_{icw}$	110.1 mEq/L
		$[Na]_{icw}$	51.9 mEq/L
Predicted Membrane Potential (Goldman)			-89 mV
Calculated pNa	0.06		

Shock

CASE 11 [redacted]

On [redacted] 1969 this 20 year old [redacted] female was admitted in the last trimester of pregnancy (EDC [redacted]) because of severe abdominal cramping pain of 14 hours duration. On admission she was noted to be vomiting fecal material. Her BP was 0/0 but quickly rose to 110/80 with the administration of Ringer's solution.

She was taken to surgery and a stillborn was delivered by Cesarean section. A volvulus was found with necrotic bowel which required an extensive resection. Surgery was over at 0430 hours on [redacted].

Signs of septic shock soon developed. BP 60/40. During this period first Muscle Transmembrane Potential was done. Average value was -71 mV. (1200 hours, 22 September). Serum $[K^+]$ 4.9 mEq/L.

She responded to treatment with antibiotics (Kantrex and Keflin) and received prednisone. On [redacted], 1969, with normal vital signs, still on antibiotics and steroids, a second Muscle Transmembrane Potential was measured and found to be -94 mV.

Four days later, she vomited blood, became shocky and required gastrectomy for stress ulcer.

The next morning ([redacted], 1969) she maintained a low BP (100/80) and a third Muscle Transmembrane Potential was measured as -79 mV.

CASE 12 [redacted]

One week previously this 23 year old [redacted] male was treated in another hospital by surgical repair of bowel perforations and splenectomy for rupture, all the result of a gunshot wound. Five days later he vomited blood, became febrile and had for the most part a low BP.

On admission BP 80/40 to 70/20. During this period of collapse which was thought to be the result of blood loss and sepsis, a Muscle Transmembrane Potential was measured as -72 mV. At the time the measurement was made, he had recently received, or was receiving Keflin, Kantrex, Penicillin and Chloromycetin. Serum $[K^+]$ = 5.5 mEq/L. Blood pH 7.37.

Five days later, with all vital signs normal, but still receiving Kantrex and Keflin his Muscle Transmembrane Potential was -89 mV. Serum $[K^+]$ = 4.0 mEq/L.

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1. Muscle is a regulated (by metabolism) sol and gel which, because of its dominate anionic charges, acts as a sump for cations. The dynamics of this attraction are such that: a) the gel preferentially captures K^+ and excludes Na^+. b) a potential difference exists between the extracellular fluid and the region within the gel. c) Changes in this potential difference, generally refered to as the Transmembrane Potential, can result from changes in extracellular concentration of ions (mainly K^+) and the total number of anionic sites on the gel. (Reference 4)

   A. In its pure form, this theory does not include a cell membrane as a structural feature. The morphologic fact that a membrane exists requires that non-structured solution on the inside of the membrane have the same or nearly the same composition as the extracellular fluid.

2. Inside muscle the regulated concentrations of K^+, Na^+ and Cl^- are the consequence of the active outward pumping of Na^+ coupled with the inward pumping of K^+. The Transmembrane Potential arises from the tendency of the ionic concentration gradients to degenerate. (References 5-8)

   A. Under such circumstances, if the membrane permeability of one ion was greatly in excess of all other ions then the Transmembrane Potential could be predicted by the Nernst Equation:

$$Em = -\frac{RT}{F} \ln \frac{[C^+]\, i^*}{[C^+]} \qquad (1)$$

B. K^+ approaches this circumstance, but its inside to outside ratio predicts too high a Transmembrane Potential for normal resting muscle when the external K^+ is normal:

$$Em = -61.5 \log \frac{[K^+]i}{[K^+].}$$

$$Em = -61.5 \log \frac{160}{45}$$

$$Em = -96 \text{ mV}.$$

C. If, however, Na^+ had a significant membrane permeability, its extracellular concentration could effect Transmembrane Potential:

$$Em = -61.5 \log \frac{[K^+]i}{[K^+]o + p\,[Na^+]o}$$

where $[Na^+]o$ is the extracellular Na^+ concentration and p is a permeability coeficient relative to the K^+ permeability. Under a variety of circumstances the value of p for $[Na^+]$ has emperically been found to be 0.01. Thus:

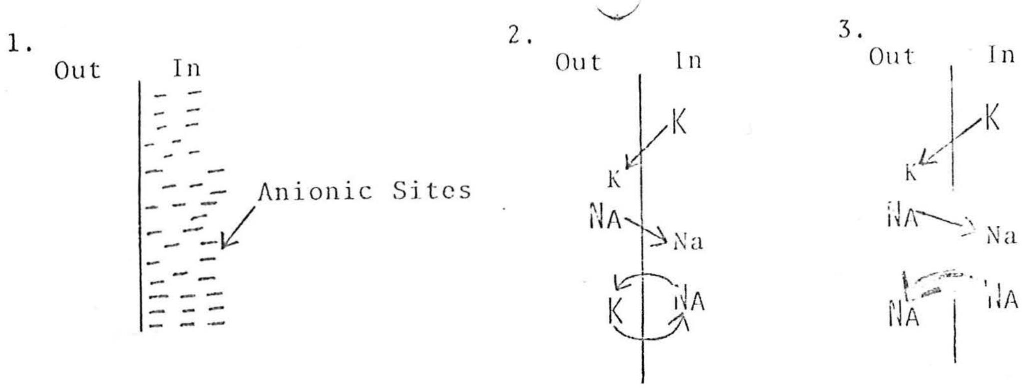
$$Em = -61.5 \log \frac{160}{4.5 + 0.01\ (145)}$$

$$Em = -88 \text{ mV}$$

* In practice, $\frac{-RT \ln 10}{F}$ is a constant at 37°C which equals -0.0615 Volts or -61.5 mV. Likewise, although the equation is concerned with ion activities, concentrations in mEq/L can be used assuming the activity coeficients of ions are the same inside and outside the cell membrane.

3. The transmembrane potential could result from an electrogenic pump which extrudes sodium from the cell. The pump sets the inside $[Na^+]$. Inside concentrations of K^+ and Cl^- are maintained relative to the potential across the membrane generated by the sodium pump. (Reference 9)

4. Finally, there may be a combination of a non-electrogenic ion exchange pump (as in 2 above) and an electrogenic outward pumping sodium pump (as in 3 above). (References 10 & 11)



Normal Human Muscle Resting Membrane Potential

Method	No. of Subjects	Membrane Potential -mV	Reference	
Surg. Expos.	4	77.8 ± 15.5(S.D.)	Johns	(14)
Surg. Expos.	--	70.0 ± 6.0(S.E.)	Norris	(15)
Surg. Expos.	1	87.4 ± 8.9(S.D.)	Creuzfeldt	(16)
Surg. Expos.	3	83.6 ± 0.5(S.E.)	McComas et al	(17)
Needle Cannula	19	87.2 ± 5.2(S.D.)	Bolte et al	(18)
Needle Cannula	9	65 ± 0.4(S.E.)	Brooks et al	(19)
Needle Cannula	16	77.5 ± 1.2(S.E.)	Goodgold et al	(20)
Needle Cannula	26	88.8 ± 3.8(S.D.)	Present Study	

Transmembrane Potential in Normal Subjects and Patients with Mild and Severe Illness

	Normal	Mild Illness	Severe Illness
Number of Subjects	26	7	21
Mean Age - years	28.9	41.9	43.8
Membrane Potential Mean ± Std. Dev.	-88.8 mV ± 3.8	-89.8 ± 2.1	-66.3 ± 9.0

Membrane Potential in Patients with Severe or Chronic Illnesses

Disease	Pt.	Age	Race	Sex	E_m (mV)
Diabetes Mellitus	[redacted]	48	W	F	-62
	[redacted]	45	C	F	-59
Uremia	[redacted]	59	C	F	-53
	[redacted]	67	C	M	-74
	[redacted]	30	W	M	-62
	[redacted]	59	C	M	-69
	[redacted]	29	L	M	-72
Malignancies	[redacted]	45	W	M	-72
	[redacted]	41	W	M	-57
	[redacted]	45	C	F	-70
	[redacted]	65	W	M	-75
Malig. HBP	[redacted]	46	W	M	-59
	[redacted]	29	W	M	-67
Thyrotoxicosis	[redacted]	20	W	M	-75
with myopathy	[redacted]	48	C	F	-79
Chronic Alcoholic	[redacted]	39	C	F	-74
	[redacted]	58	C	F	-65
Scleroderma	[redacted]	45	C	F	-67
Polyneuropathy	[redacted]	24	W	M	-80
Polymyositis	[redacted]	33	W	F	-53
Myocardiopathy	[redacted]	40	W	F	-48

Resting Muscle Potential and Intracellular Electrolyte Composition in Normal Subjects and Severely Ill Patients

Group and Number of Individuals	Measured Em	Intracellular Composition			Extracellular Water	Extracellular Composition+		
		Na+	K+	Cl⁻		Na+	K+	Cl⁻
	mV	mEq/L	mEq/L	mEq/L	% Wet Wt.	mEq/L	mEq/L	mEq/L
Normal Subjects (7)	-89 ± 2.9*	26.5 ± 4.3	149.0 ±13.6	4.1 ±1.5	26.6 ± 4.2	134.8 ±5.6	4.1 ±0.4	104.4 ±5.7
Severely Ill Patients (13)	-67 ± 8.6	37.7 ±10.1	151.5 ±18.6	8.8 ±3.6	24.2 ±11.9	135.5 ±3.9	4.3 ±0.7	106. ±4.

* Mean and Std. Dev.

\+ Plasma values corrected for Donnan effect and water content.

Red Blood Cell Sodium and Potassium

24 Normal Controls	[Na+] mEq/L	[K+] mEq/L
	7.5 ± 2.0	96.4 ± 4.0

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