



Endocrinology, energetics, and human life history: A synthetic model

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1 **Endocrinology, Energetics, and Human Life History: A Synthetic Model**

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8

9 ***Abstract***

10

11

12 Human life histories are shaped by the allocation of metabolic energy to
13 competing physiological domains. A model framework of the pathways of energy
14 allocation is described and hormonal regulators of allocation along the pathways of the
15 framework are discussed in the light of evidence from field studies of the endocrinology
16 of human energetics. The framework is then used to generate simple models of two
17 important life history transitions in humans, puberty and the postpartum return to full
18 fecundity in females. The results of the models correspond very closely to observations
19 made in the field.

20

21

22

23 Introduction

24

25 The essence of life can be defined as “metabolism in the service of
26 reproduction.” Organisms capture energy from the environment and turn it into more
27 organisms. Natural selection has favored those variations that perform this task more
28 reliably and more efficiently than their competitors. But the route from energy capture to
29 reproduction can be complex. Even in the simplest organisms some captured energy
30 must be devoted to growth and maintenance of the organism as well as to reproduction.
31 Reproduction without growth would rapidly lead to smaller and smaller organisms until
32 the size limits of viability were reached. Investment in maintenance leads to increased
33 survivorship and opportunities to continue reproducing. The partitioning of available
34 energy among these non-overlapping categories gives rise to the patterning of life
35 histories -- variation in age-specific probabilities of mortality and fertility, trajectories of
36 growth, rates of senescence, and other aspects of phenotype that are only manifest in a
37 diachronic view, in the way an organism’s life unfolds rather than in its state at any
38 given time.

39

40 Life history theory emphasizes trade-offs and how optimal energy allocation
41 varies with age and environmental circumstances. But this body of theory often leaves
42 unspecified the physiological mechanisms that govern and regulate those trade-offs.
43 The field of human reproductive ecology has emerged out of an effort to understand
44 those mechanisms as they relate to the regulation of reproductive effort in particular

45 (Ellison, 2003a, 2009). More recent efforts to illuminate the mechanisms governing
46 trade-offs of investment in growth and immune function are helping to further advance
47 an integration of the physiological mechanisms of energy allocation decisions with the
48 conceptual framework of life history theory (Flatt and Heyland, 2011). The focus of this
49 paper will be a consideration of the ways the endocrine system helps to regulate
50 metabolic energy allocation to generate the structure of human life history.

51

52 The endocrine system is one of the three major systems of integration of
53 vertebrate physiology based on molecular communication, the other two being the
54 nervous system and the immune system. The power of the endocrine system as a
55 physiological integrator lies in two properties: (i) the diffuse nature of its communication,
56 reaching all cells of the organism, and (ii) its ability to regulate both cellular activity and
57 gene expression. Together these properties position the endocrine system to regulate
58 energy allocation in ways that integrate with developmental and life history changes.

59

60 There are, however, two frequent biases in endocrinology that we should be
61 particularly aware of in considering the regulation of metabolic energy allocation: the
62 “top down bias” and the “newcomer bias.” The top down bias is manifest in a
63 predilection for assuming that the brain is in charge of the body. In many areas this is
64 true, but it is not an absolute hierarchy of regulation. Elsewhere (Ellison, 2009) I have
65 noted that molecular communication can be classified by the channels through which it
66 flows into (a) central-nervous-system (CNS)-to-soma, (b) soma-to-CNS, (c) soma-to-

67 soma, and, (d) CNS-to-CNS. Behavioral endocrinology is dominated by soma-to-CNS
68 communication, coordinating behavior with the physiological state of the organism,
69 particularly as regards the regulation of reproductive effort. The most potent
70 messengers along this pathway are those that easily cross the blood-brain barrier,
71 especially steroids, as well as peptides that gain access to the basal hypothalamus.
72 CNS-to-soma communication primarily flows through the hypothalamic-pituitary
73 “transducer”, integrating sensory and other information from basal ganglia and higher
74 cortical areas in the regulation of peripheral organs and endocrine glands. Larger
75 protein molecules are typical messengers along this pathway. Both the soma-to-CNS
76 and CNS-to-soma channels can have important effects on the allocation of metabolic
77 energy. But the primary conduit for messages regulating energy allocation is the soma-
78 to-soma channel. This pathway includes messengers of all chemical types, including
79 steroids (both gonadal and adrenal), thyroid hormones, proteins (including pancreatic
80 hormones), and peptides (including gut hormones and adipokines). In large part, as will
81 be described, the action of messages flowing through the CNS-to-soma pathway on
82 energy allocation is achieved by modifying the action of messages in the soma-to-soma
83 pathway.

84

85 The newcomer bias is manifested in a natural fascination with newly discovered
86 or described messenger molecules and the desire to see them as particularly important
87 in their effects. This can often be the case, but should not cause us to neglect the
88 central roles that are often played by those messengers who have long featured in our

89 understanding of endocrine physiology. Many of these, such as steroids, thyroid
90 hormones, pancreatic and gut hormones, also feature prominently in the soma-to-soma
91 channel.

92

93 Keeping these biases in mind, we can consider the major features of the
94 endocrine regulation of energy allocation decisions and their impact on human life
95 history. The framework described here will necessarily be an over-simplification, like all
96 models. Yet hopefully it will capture enough of the important features of the system to
97 be heuristic, in organizing and synthesizing information, in illuminating complex
98 interactions and processes, and in generating hypotheses. Where possible, we will pay
99 attention to evidence from and applications to field studies of human physiology.

100

101 *The endocrine framework of human energetics*

102

103 The basic framework of human energetics, the flow of energy through the
104 organism, is represented by the diagram in Figure 1 where the pathways indicated by
105 specific arrows are associated with the hormonal regulators shown in Figure 2. As a
106 model, not all the pathways of physiological integration and regulation that affect
107 energetics are included, nor all the potential endocrine signals involved. Those that are
108 included are considered to be major pathways and regulators which account for major
109 aspects of energy allocation and its life history effects.

110

111 At the center of the framework is “available metabolic energy,” available for
112 immediate allocation to any one of a number of non-overlapping categories. Inputs to
113 available metabolic energy come either from direct intake, or from stores, filtered by the
114 regulation of ATP production. The major allocation categories for available metabolic
115 energy are identified as storage, activity, anabolism, and maintenance. Anabolic sub-
116 categories include growth and reproduction. The parts of this framework will be
117 considered in turn.

118

119

120 Regulation of energy balance

121

122 Energy balance refers to the difference between energy intake through nutrition
123 and energy expenditure through all metabolic pathways. Of the various pathways of
124 energy expenditure, physical activity can be separated out as distinct from those that
125 contribute to resting metabolic rate. The net of energy intake and expenditure in activity
126 can be considered as the contribution to available metabolic energy from the
127 environment.

128

129 Energy intake is not tightly regulated by the endocrine system, since it depends
130 greatly on environmental factors. Appetite regulation, however, is strongly affected by
131 endocrine signals (Badman and Flier, 2005; Blundell et al., 2015a; Blundell et al.,
132 2015b; Crespo et al., 2014; Meier and Gressner, 2004; Schwartz, 2000; Schwartz et al.,

133 2000; Webber et al., 2015). Two signaling molecules that will be considered in this
134 model are leptin and ghrelin. Both are peptides, principally produced in the soma but
135 capable of some penetration of the blood-brain barrier. Leptin is primarily produced by
136 adipocytes, ghrelin by the gut. Both carry information to the hypothalamus that can
137 affect appetite. Leptin, a tonic hormone reflecting the mass of adipocytes, is associated
138 with reduced hunger when circulating levels are high and increased hunger when levels
139 are low (Schwartz et al., 2000). Ghrelin, an episodic hormone which reflects short-term
140 status of gut contents, with high levels occurring when the gut is relatively empty for an
141 extended period, stimulates hunger when its levels are high (Pinkney, 2014). These
142 orexigenic effects are mediated by and coordinated with other neural signaling, primarily
143 in the ventromedial hypothalamus (Webber et al., 2015).

144

145 Energy expenditure in activity is not under tight hormonal control in humans, but
146 in rodent models, lowered leptin levels were early observed to correlate with increased
147 levels of physical activity, perhaps reflecting a stimulation of the motivation to forage for
148 food (Pellemounter et al., 1995; Wolf, 1996). In many rodents, food foraging exposes
149 the animal to significant predation risk. Appetite regulation may serve to help regulate
150 foraging effort in a way that balances risks versus benefits. There is no evidence at this
151 time that foraging effort in human hunter-gatherer societies (the evolutionarily salient
152 human subsistence pattern) or any other ecological context is related to hormonal
153 appetite regulation. However, there is clinical evidence that exercise may affect
154 appetite through the mediation of appetite regulating hormones (Blundell et al., 2015b).

155

156 Studies of human leptin and ghrelin levels in the field have produced some
157 notable results, particularly highlighting population variation in average levels
158 (Bribiescas, 2001, 2005; Bribiescas and Hickey, 2006; Kuzawa et al., 2007; Miller et al.,
159 2006; Munch-Andersen et al., 2013; Sharrock et al., 2008; Tanaka et al., 2005). In
160 general, subjects in non-western populations and populations engaged in subsistence
161 economies have significantly lower levels of both appetite regulating hormones than in
162 western, developed societies. This is true for leptin even after correcting for fat mass.
163 At the least this suggests that caution needs to be exercised in interpreting the
164 significance of absolute levels of these hormones. It is likely that the set-points for
165 appetite regulation may be influenced by developmental factors (Sharrock et al., 2008)
166 and may reflect population differences in overall energy budgets.

167

168

169 *Regulation of energy availability*

170

171 *a. Release of oxidizable substrates*

172

173 Oxidizable substrates (principally carbohydrates and fatty acids) are released
174 from stores into the blood stream under the regulation of several different hormones.
175 Among the most important regulators of energy substrate release in humans are
176 cortisol, epinephrine, and glucagon. Epinephrine and glucagon are relatively short-term

177 regulators, involved in defending blood sugar homeostasis against the vagaries of
178 intake and expenditure on a time scale of minutes to hours. Because of their short-term
179 effects, these hormones are often involved in behavioral responses, including “fight or
180 flight” scenarios. However, they are not directly implicated in the longer term regulation
181 of energy substrate release that is typically involved in life history strategies and
182 transitions.

183

184 Cortisol, on the other hand, is involved in longer term regulation of energy
185 substrate availability. Cortisol has been associated with responses to psychosocial
186 stress, to the extent that it is frequently referred to as a “stress” hormone. However, it
187 can be misleading to label cortisol in this way, since psychosocial stress is only one
188 potential trigger for its release. Other than categorizing cortisol by one of the multiple
189 factors that can cause its release, it would be better to categorize it by its downstream
190 effects as a “metabolic” hormone. Cortisol’s principal actions involve the stimulation of
191 lipolysis to release fatty acids from adipose stores and the antagonism of
192 gluconeogenesis, resulting in an increase in available oxidizable substrates (Widmaier
193 et al., 2013). Although cortisol is elevated as a consequence of short-term stresses, it
194 rapidly returns to baseline when those stresses are removed. Chronic energy
195 demands, as can occur with infection and undernutrition (or, in other animals, migration
196 and hibernation), can result in chronically elevated cortisol and a shift toward greater
197 reliance on stored energy reserves. Shifts in chronic cortisol release also occur with

198 reproductive state in human females, being elevated during pregnancy to mobilize
199 maternal fat reserves to support fetal growth (Widmaier et al., 2013).

200

201 It should be noted that while cortisol promotes the release of free fatty acids via
202 lipolysis, it does not stimulate the beta oxidation pathway by which fatty acids gain entry
203 to the tricarboxylic acid cycle (Widmaier et al., 2013) Pathological elevation of cortisol
204 without increased energy expenditure, as in Cushing's syndrome, can result in
205 excessive fat accumulation in adipose depots and ectopic locations less sensitive to
206 cortisol action and thus be associated with redistribution of fat rather than loss of fat
207 (Despres and Lemieux, 2006).

208

209 In part because cortisol is readily measured in saliva and urine, as well as in
210 blood, there are numerous field studies of human cortisol. Many studies focus on short-
211 term cortisol dynamics in relation to psycho-social stress. Field studies of longer term
212 effects have focused on immune function, pregnancy, and lactation (Cohen et al., 2012;
213 Janicki-Deverts et al., 2016; Nepomnaschy et al., 2006; Oaks et al., 2016; Valeggia and
214 Ellison, 2004; Valeggia and Ellison, 2003).

215

216 *b. Efficiency of ATP production*

217

218 At the cellular level the utilization of oxidizable substrates is auto-regulated by the
219 accumulation of downstream products, and thus ultimately driven by energy

220 expenditure. However, basal metabolic rate, the baseline turnover of energy substrates
221 in the body, is itself subject to hormonal regulation. Among the most potent regulators
222 of basal metabolism are the thyroid hormones, especially thyroxine (T4). Under
223 conditions of chronic energetic stress, such as fasting and starvation, T4 is lowered,
224 resulting in a lower baseline rate of energy consumption by the body (McAninch and
225 Bianco, 2014).

226

227 Up-regulation of T4 production can be part of an adaptive response to cold stress
228 (Leonard et al., 2005; Leppaluoto et al., 2005). The efficiency of ATP production by the
229 mitochondrial electron transport chain in some tissues, particularly brown fat, is
230 regulated by T4 through the up-regulation of uncoupling protein (UCP) (Busiello et al.,
231 2015; Leppaluoto et al., 2005). UCP decouples the return flow of hydrogen ions across
232 the mitochondrial inner membrane from ATP production, resulting in an increased
233 production of heat. UCP is particularly abundant in brown adipose tissue which can
234 assist in the regulation of core body temperature, particularly in infants. Field studies of
235 high latitude populations have also demonstrated seasonal shifts in T4 production and
236 basal metabolism in adults associated with recurrent cold stress, a response that
237 appears to be greater in populations native to high latitudes than to more recent
238 migrants (Leonard et al., 2014; Levy et al., 2013; Tkachev et al., 1991).

239

240

241 Insulin-independent maintenance effort

242

243 Energy allocation is organized hierarchically. Wade and Jones (Wade and
244 Jones, 2004) schematically represent this hierarchy in three levels: functions that must
245 be maintained at or near normal levels at all times; functions that can be down-
246 regulated at need, but cannot easily be interrupted for long periods; and functions that
247 can be interrupted at need for extended periods. The top priority functions include the
248 maintenance of brain function via the constant maintenance of membrane
249 depolarization as well as indispensable vegetal activities such as heart and respiratory
250 function, and some aspects of kidney and liver function. Mid-level priority functions
251 include physical activity, immune function, and protein anabolism. Dispensable or
252 interruptible functions include growth and reproduction, although these are also subject
253 to mid-level down-regulation as well as interruption.

254

255 Reproductive state can reorganize this hierarchy somewhat in females. During
256 pregnancy and lactation fetal growth and infant nutrition assume relatively high
257 priorities, at or near the top level. The interruption of female fecundity by pregnancy
258 and early lactation can be viewed as evidence of the priority of the fetus and infant over
259 lower level maternal priorities. The down-regulation of maternal basal metabolism that
260 can occur during pregnancy and lactation when energy availability is limited, noted
261 above, can be seen as evidence of the higher metabolic priority assigned to the fetus
262 and infant than mid-level priorities of the mother.

263

264 Top-level metabolic priorities are largely insulin-independent (Fernandez-Real
265 and Ricart, 2003). The brain and fetus are particularly clear examples of insulin-
266 independent substrate uptake. Energy flow to these priorities is regulated only by the
267 availability of oxidizable substrates in the blood. The role of cortisol, glucagon, and
268 epinephrine can be best understood as buffering energy flow to top-level functions.
269 That is, when energy demands increase at lower levels, such as those precipitated by
270 “fight or flight” scenarios, these hormones increase the levels of oxidizable substrates in
271 the blood so that the new demands can be met without compromising top-level
272 functions. Down-regulation of competing demands for oxidizable substrates can also
273 increase their availability for top level functions. Physiological responses to fasting and
274 starvation, for example, include down-regulation of mid-level and low-level functions to
275 free up energy for the top priority functions (Keys et al., 1950).

276

277 *Energy allocation to storage and anabolic effort*

278

279 In textbooks the role of insulin at the organismic level is most often presented in
280 terms of glucose homeostasis, its function being to stimulate the clearance of excess
281 circulating glucose (Widmaier et al., 2013). But this is a poor and incomplete
282 characterization of its function. Insulin does not simply facilitate removal of glucose
283 from the blood, a function also performed by the kidney. It stimulates the uptake of
284 glucose by target tissues especially for storage in adipose tissue and to support protein
285 anabolism. Insulin also stimulates mitotic activity in many target tissues which, in

286 conjunction with its anabolic effects, can promote cellular proliferation and tissue growth
287 (Sandow, 2009).

288

289 Viewed in these terms, the key role of insulin is to promote energy allocation to
290 medium and low priority metabolic functions on a facultative basis, not simply the
291 regulation of circulating glucose levels. When metabolic energy is available in excess of
292 high and mid-level category requirements, insulin promotes the diversion of the excess
293 either to storage or to anabolism. Similarly, the “counter-regulatory hormones” cortisol,
294 glucagon, and epinephrine, do not simply counter-balance the effects of insulin on blood
295 glucose, but buffer the flow of energy to top-level metabolic functions from fluctuations
296 in intake and lower level demands independently of insulin. The balance of these
297 hormones results in the hierarchical regulation of energy flow within the body, not simply
298 in the avoidance of the pathological consequences of hyperglycemia.

299

300 Insulin was one of the first protein hormones to be isolated, characterized, and
301 used therapeutically, due to its clinical importance in the pathogenesis and treatment of
302 diabetes mellitus (Sanger and Tuppy, 1951a, b). In this context, a great deal is known
303 about short-term insulin dynamics in relation to changes in blood glucose. But recently
304 a new approach, based on measurement of C-peptide of insulin in urine, has been
305 utilized to study longer-term changes in baseline insulin levels under field conditions
306 and not in the context of disease (Sherry and Ellison, 2007). C-peptide of insulin is a
307 section of the pro-insulin molecule that is cleaved in the production of active insulin. It is

308 produced in a 1:1 ratio to active insulin and is cleared intact into the urine. Thus
309 measurement of urinary C-peptide, indexed by time, creatinine, or specific gravity, can
310 be used as a proxy measurement of insulin production. Urinary C-peptide measured in
311 samples collected in the field has been used to study longitudinal and cross-sectional
312 variation in energy balance in Samoa (Sherry and Ellison, 2007; Sherry et al., 2014),
313 Argentina (Ellison and Valeggia, 2003; Valeggia and Ellison, 2001, 2004; Valeggia and
314 Ellison, 2003), and The Gambia (Reiches et al., 2013; Reiches et al., 2014), among
315 other settings.

316

317

318 *Biasing of energy allocation towards growth effort*

319

320 Insulin controls energy allocation to lower priority metabolic categories, including
321 energy storage, and the anabolic categories growth and reproduction. The triage of
322 energy allocation among these competing categories, however, is largely under the
323 control of a trio of phylogenetically related protein hormones: growth hormone (GH),
324 prolactin (PRL), and human placental lactogen (hPL). The genes for growth hormone
325 and human placental lactogen are both located on chromosome 17 and display ~96%
326 sequence homology, indicating common ancestry through a gene duplication event.
327 PRL is more distantly related, located on chromosome 6 and displaying ~ 85%
328 sequence homology with GH. GH and PRL are both synthesized and secreted by
329 acidophilic cells of the anterior pituitary, while the hPL gene is expressed in the

330 placenta. All three hormones have suppressive effects on whole body insulin
331 sensitivity, primarily through an inhibition of glucose uptake by somatic adipose tissue.
332 At the same time, however, all three synergize with insulin in promoting anabolic
333 processes in target tissues: accumulation of skeletal and lean body mass in the case of
334 GH, mammary gland glucose uptake and milk synthesis in the case of PRL, and fetal
335 glucose transfer and fetal growth in the case of hPL (Forsyth and Wallis, 2002; Goffin et
336 al., 1996; Wallis et al., 2005).

337

338 The secretion of these hormones varies with maturational and reproductive
339 status, resulting in the differential allocation of available metabolic energy among these
340 anabolic categories. GH follows a steep decline following birth as the high rate of infant
341 growth declines to low levels in mid-childhood, but it undergoes an endogenous rise in
342 puberty, serving to promote skeletal and lean body growth (Bona et al., 1999; Rose et
343 al., 1991). At the same time, by increasing insulin resistance in adipose tissue it limits
344 energy allocation to storage and causes a transient rise in basal insulin levels (Guercio
345 et al., 2002). hPL by the placenta increases through pregnancy, elevating insulin
346 resistance in the mother and increasing the flow of metabolic energy to the fetus
347 (Braunstein, 2003; Mesiano and Jaffe, 2004). PRL production during lactation is
348 stimulated by infant nursing demand and acts to promote the uptake of glucose and
349 fatty acids by the mammary gland and the production of milk. At the same time it
350 increases insulin resistance in maternal adipose tissue, resulting in a diversion of
351 metabolic energy to milk production (Molitch, 2004).

352

353 There is a long history of measuring prolactin in field studies of lactation (see
354 (Ellison, 1995) and growth hormone in studies of human growth (see Bogin, 1999).
355 Studies of hPL are confined to clinical settings.

356

357

358 *Energy allocation to reproductive effort*

359

360 Energy allocation to reproductive effort is primarily reflected and governed by
361 gonadal steroids (Ellison, 2003b). In females, ovarian steroids directly modulate
362 fecundity, influence sexual attractiveness to males as well as receptive and proceptive
363 sexual behavior, and promote energy storage in adipose tissue (an important form of
364 somatic reproductive effort in females). In males, testosterone maintains sperm
365 production, stimulates libido and mating effort and may also support increased social
366 confidence and assertiveness, and promotes increases in muscle mass (an important
367 form of somatic reproductive effort in males).

368

369 The production and release of gonadal steroids is governed by the gonadotropin
370 hormones, follicle stimulating hormone (FSH) and luteinizing hormone (LH) secreted by
371 the anterior pituitary. However, the effectiveness of this gonadotropin stimulation
372 depends strongly on insulin, so strongly that insulin is sometimes characterized as a co-
373 gonadotropin (Poretsky et al., 1999; Poretsky and Kalin, 1987). This effect has been

374 mostly clearly demonstrated in *in vitro* studies of steroid production by cultured ovarian
375 granulosa cells, where insulin receptor has been identified as the mediator of the effect,
376 increasing the rate of steroid production per cell.

377

378 Gonadal steroids, in their turn, synergize with insulin in promoting somatic
379 reproductive effort in both sexes, promoting increases in muscle mass in males
380 (androgens) and increases in adipose mass in females (estrogens) (Grumbach and
381 Styne, 2003). The mutual synergies between insulin and gonadal steroids constitute a
382 positive feedback loop that can dramatically up-regulate the flow of metabolic energy to
383 reproductive effort to take advantage of conditions of positive energy balance and the
384 availability of metabolic energy in excess of the needs of high priority categories.

385

386 The advent of practical methods for assaying gonadal steroids in saliva (Ellison,
387 1988; Lipson and Ellison, 1989), in addition to blood and urine, led to a rapid increase in
388 the number of field studies of gonadal steroids in human populations. Many examples
389 are provided elsewhere in this issue.

390

391 *Hormonal gating of energy allocation*

392

393 The hormonal framework described above governs the allocation of available
394 metabolic energy to competing domains in a hierarchical way. Top priority metabolic
395 categories, including brain and vegetal physiology, as well as fetal growth and infant

396 nutrition during pregnancy and lactation, receive energy in direct proportion to its
397 availability. That availability is determined by the hormones that mobilize oxidizable
398 substrates and those that govern the rate and efficiency of ATP production as well as by
399 the competing demands of physical activity.

400

401 Insulin controls the gate for allocation of energy to lower level, “dispensable”
402 categories such as energy storage, growth, and reproduction. Cortisol opposes this
403 allocation, increasing the availability of metabolic energy to mid-level categories such as
404 immune function as well as buffering top level allocations. Allocation of metabolic
405 energy among potentially competing lower level categories is governed by GH, PRL,
406 hPL, and gonadal steroids interacting with and modifying the action of insulin.

407

408 The dynamic interaction of the key hormones governing energy allocation helps
409 to organize key life history transitions. Puberty and postpartum resumption of ovarian
410 function are two particularly clear examples and will be considered here in some detail.

411

412 *The pubertal transition*

413

414 Puberty involves a transition in energy allocation from growth to adult
415 reproductive potential during which the body is modified, sexual dimorphism is
416 elaborated, and reproductive potential is established (Ellison et al., 2012). Although not
417 as dramatic as the metamorphosis of holometabolous insects or most amphibians, it is

418 the human equivalent, changing juvenile morphology to a distinctively adult pattern and
419 elaborating immature, nonfunctional reproductive organs into mature, functioning ones.
420 Puberty involves the close coordination of primary reproductive maturation with the
421 rapid growth and transformation of the body. Reproductive maturation involves the
422 appearance (or, more properly, reappearance) of pulsatile release of gonadotropin
423 releasing-hormone (GnRH) by the median eminence of the hypothalamus, which in turn
424 stimulates increased production of FSH and LH (Grumbach and Styne, 2003). The
425 factors that determine this change in GnRH production are still incompletely understood,
426 but the change begins quite early, well before internal or external manifestations of
427 increasing gonadal activity. The skeletal growth spurt that is typical of puberty is
428 primarily caused by an endogenous increase in GH and its downstream consequences
429 (Grumbach and Styne, 2003). Again, the causes of the increase in GH secretion are
430 incompletely understood, but its timing is roughly synchronous with the first appearance
431 of pulsatile gonadotropin secretion, suggesting a linkage between the two events (Suter,
432 2004; Gahete et al., 2016). The elaboration of somatic sexual dimorphism results from
433 the interaction of pubertal growth with rising titers of gonadal steroids. Differential
434 growth between the sexes resulting in adult sexual dimorphism is mediated by gonadal
435 steroids, both androgens and estrogens (Ellison et al., 2012).

436

437 The hormonal management of energy allocation during the pubertal transition
438 can be sketched out in terms of the framework described above. We assume that the
439 process is set in train when pulsatile GnRH reappears and GH begins to rise, even if the

440 direct causes of those two events remain to be fully understood. Rising levels of GH
441 stimulate growth and divert energy away from storage. The elevated GH also results in
442 increasing insulin resistance in adipose tissue, causing basal levels of insulin to rise.
443 Rising insulin would synergize with the increasing gonadotropin titers resulting from
444 increasingly stable GnRH pulses to promote gonadal steroid production and release.
445 As they approach mature levels, gonadal steroids in turn will potentiate the peripheral
446 effects of insulin, leading to a shift back toward lower insulin levels and increased
447 energy allocation to fat storage (in females) and muscle mass (in males), now as
448 sexually dimorphic forms of somatic reproductive effort. Even as they shift the direction
449 of energy allocation, gonadal steroids cause the closure of epiphyseal growth plates
450 and the cessation of skeletal growth as well as causing the remodeling of the female
451 pelvis.

452

453 In this way the pubertal transition unfolds as an endogenous process governed
454 by the interaction of the endocrine framework of energy allocation and its integration
455 with the growth and maturational processes involved. Energy allocation is first diverted
456 away from storage to support somatic growth and transformation and then returned to
457 storage as well as sexually dimorphic somatic forms of reproductive effort. A
458 characteristic and transient period of hyperinsulinemia is a central part of the process,
459 helping to accelerate gonadal steroid production to its mature levels. The mature
460 steroid levels in turn resolve the transient insulin resistance.

461

462 This schema is consistent with observations of shifting energy allocation priorities
463 in female Gambian adolescents (Reiches et al., 2014). In the midst of the pubertal
464 transition, when skeletal growth is still underway, Gambian girls will respond to periods
465 of energetic stress by defending lean body mass at the expense of fat mass, but later in
466 the process as skeletal growth comes to a halt the same periods of energetic stress are
467 associated with a defense of fat mass at the expense of lean body mass. The
468 metabolic priority given to growth early gives way to a metabolic priority of somatic
469 reproductive effort late (Figure 3).

470

471 *A mathematical model of the pubertal transition*

472

473 The smooth, autonomous nature of the transition can also be demonstrated in a
474 quantitative model of female puberty. The specifics of the model are provided in
475 Supplementary Materials. The point of the model is to demonstrate that the interactions
476 between the principal hormonal regulators reviewed above act like interlocking gears,
477 so that changes in one component drive changes in the system as a whole. The shape
478 of the changes that ensue is a function of the feedback links within the system. The
479 central set of interactions are those between insulin directing energy to anabolic effort,
480 the pituitary proteins (prolactin, growth hormone, placental lactogen) biasing energy to
481 growth effort and feeding back on insulin through their effects on somatic insulin
482 resistance, and the gonadal steroids (estradiol, progesterone, and testosterone) biasing
483 energy to reproductive effort and feeding back negatively on the pituitary proteins

484 regulating growth effort. Because the interactions of these hormones are interlocking,
485 the system as a whole can be changed by changes in any one of the components. But
486 the nature of the interactions causes the system to “switch” from a bias toward growth
487 effort to a bias toward reproductive effort, a switch that reflects the essential nature of a
488 life history transition as defined in this paper. Both the transition from growth to
489 reproduction at puberty (described here) and the resumption of ovarian function
490 postpartum (described below) can be modeled by the same system of interactions.

491
492 The assumptions and parameter settings of the quantitative models are meant to
493 be as simple as possible. In the model of the pubertal transition, GH is assumed to be
494 the independent driving factor, with all other variables dependent on it. In fact, the
495 initiation of the GH rise remains something of a mystery. There is mounting evidence
496 suggesting that the rise in GH may be tied to the same neural mechanisms, including
497 kisspeptin signaling to the pituitary, that disinhibit GnRH pulsatility in the hypothalamus
498 (Gahete et al., 2016). This would suggest that the initiation of the GH rise and the
499 nocturnal, sleep-associated appearance of pulsatile LH may be more or less coincident
500 (Apter, 1997, Suter 2004). In any event, increases in GH ordinarily precede detectable
501 increases in gonadal steroids (Rogol, 2010). So in this model the assumption is made
502 that a rise in GH starts the transition.

503
504 GH is assumed to fall steeply with age prior to puberty in parallel with growth
505 velocity (Bona et al., 1999; Rose et al., 1991; Chemaitilly et al., 2003), according to a

506 rational function (a simple mathematical expression for a pattern of smooth, asymptotic
507 decline (Otto and Day, 2007), with an endogenous, normally shaped rise and fall
508 beginning at about age 8 years and centered on age 12.5 years. These ages are
509 arbitrary, but are chosen to reflect contemporary observations of adolescent growth for
510 females in the US and other developed nations where high quality longitudinal data are
511 available (Kuczmarski et al., 2002). For males, the age parameters can be set
512 approximately two years later. The normal shape of the GH rise during puberty is an
513 arbitrary assumption that generally reflects the observed pattern (Albertsson-Wikland et
514 al., 1994). The exact shape of the trajectory isn't important to the model; what is
515 important is that GH undergoes a rise at puberty before falling to adult levels.

516

517 Insulin, *independent of the effect of GH*, is assumed to follow a slow logistic rise
518 from childhood to adult levels (Ballerini et al., 2016). However, the effect of GH on
519 insulin resistance, assumed to be proportional to the level of GH, results in a transient
520 increase in insulin. Estradiol, *in the absence of insulin*, is assumed to follow a slow
521 logistic rise to adult levels, becoming noticeable (about 10% of adult levels) at about the
522 same time as the start of the GH rise, driven by gonadotropin levels that are themselves
523 responding to the resumption of pulsatile GnRH release. The logistic form of the
524 estradiol trajectory is arbitrary but is a simple mathematical form that can be used to
525 model sigmoid patterns (Otto and Day, 2007). A dummy factor ("lag") is introduced to
526 center the inflection point of the estradiol at about 12.5 years (around the time of
527 menarche) and an asymptotic approach to adult levels at around 20 years. This pattern

528 reflects empirical observations indicating continued increases in ovarian function for a
529 number of years after menarche until at least the late teens/early twenties (Lipson and
530 Ellison 1992, Ellison 1996). Under the stimulating influence of insulin, assumed to be
531 proportional to insulin level, the rise in estradiol becomes steeper and overshoots final
532 adult levels slightly before converging on them in the late teens. Growth rate is
533 assumed to be proportional to GH levels, minus a braking effect assumed to be
534 proportional to estradiol levels, resulting from the action of estradiol in accelerating the
535 closure of the epiphyses of the long bones. The braking effect of estradiol results in a
536 more rapid deceleration of growth that reaches its steepest decline at about the time of
537 menarche. The resulting pattern is represented in Figure 4. As noted above, the
538 parameters have been arbitrarily set to reflect the timing of puberty similar to that in the
539 US and other industrialized populations. Delay in the initial rise in GH would shift the
540 entire pattern to the right, typical of later puberty. Substitution of testosterone for
541 estradiol, together with a later onset of the GH rise, would generate a model typical of
542 males. Note that testosterone conversion to estradiol in the growth plates results in the
543 same braking effect on linear growth as in females. Note also that the model does not
544 specify exact hormone levels, but only relative levels, with 1.0 representing typical adult
545 values.

546

547 *The postpartum resumption of ovarian function*

548

549 A second example of the hormonal orchestration of a life history transition is the
550 postpartum resumption of ovarian function. In this case, a transition occurs between
551 energetic allocation to milk and energetic investment in fecund reproductive capacity.
552 The transition unfolds in a manner very reminiscent of the pubertal transition, with PRL
553 taking on the role played by GH during puberty. In a lactating mother early in the
554 postpartum period milk production assumes a high priority. It is driven by PRL secretion
555 which is responsive to infant demand but also reflective of maternal energy availability
556 (Ellison, 1995). When infants are exclusively breastfed by mothers facing energetic
557 constraints, PRL levels will be high and insulin levels low. PRL directs energy toward
558 milk production by increasing the insulin resistance of peripheral maternal adipose
559 tissue (though there is also evidence that PRL increases insulin sensitivity in mammary
560 adipose tissue). Gonadal activity is extremely low, though FSH levels are near normal
561 (McNeilly et al., 1994), suggesting ovarian resistance to gonadotropin stimulation.

562

563 Later in the postpartum period PRL levels begin to decline. This occurs most
564 often as a consequence of the introduction of supplementary foods into the infant's diet
565 (McNeilly et al., 1994), reducing the demand for milk. Reduced energy demand for milk
566 production results in increased energy availability to the mother and rising levels of
567 basal insulin. Energy allocation to storage rises as a consequence, but PRL levels
568 remain sufficient to cause elevated insulin resistance. As a result, insulin levels rise
569 above the typical level for the mother, manifesting a brief, transient period of
570 hyperinsulinemia. This transient period of hyperinsulinemia, although briefer in

571 duration, is very reminiscent of the transient period of elevated insulin in puberty. The
572 elevated insulin synergize with FSH levels to stimulate ovarian steroid production
573 toward normal mature levels. The rising titers of estradiol that result in turn potentiate
574 energy storage in adipose tissue, increasing adipose insulin sensitivity and returning
575 insulin levels to normal.

576

577 As with the pubertal transition, the resumption of postpartum ovarian function is
578 governed endogenously by the endocrine architecture of energy allocation. Insulin once
579 again plays a central role, modified by the actions of PRL and gonadal steroids. The
580 unfolding sequence is clearly displayed by Toba mothers in Argentina (Ellison and
581 Valeggia, 2003; Valeggia and Ellison, 2001, 2004; Valeggia and Ellison, 2003) (Figure
582 5), and a comparable pattern has even been observed in wild chimpanzees in Uganda
583 (Emery Thompson et al., 2012).

584

585 *A mathematical model of the postpartum resumption of ovarian function*

586

587 As with the pubertal transition, the smooth, endogenous nature of the resumption
588 of ovarian function postpartum can be represented in a qualitative model (details in
589 Supplementary Materials). This model includes analogous hormonal interactions to
590 those presented in the puberty model above. In this case, PRL level is assumed to be
591 the independent driving factor with other variables being dependent on it. Prolactin is
592 assumed to decline following a logistic function (a simple expression for a sigmoid

593 pattern, Otto and Day, 2007) and to represent the energy demand for milk production.
594 In the version of the model presented here the decline in PRL is parameterized to return
595 to baseline by 40 months with a maximal rate of decline at 18-20 months. This is an
596 arbitrary parameterization designed to reflect patterns observed in the Toba (Valeggia
597 and Ellison, 2004). Different values for the parameters of the logistic could be chosen
598 to reflect earlier or later weaning or other factors affecting energy availability. Energy
599 availability for lower level priorities than milk production is assumed to be proportional to
600 the complement of PRL (where peak PRL is set at 1.0 as a reference). Insulin is
601 expected to be proportional to energy availability, but modified by the insulin resistance
602 caused by prolactin. If insulin sensitivity were constant, insulin levels would rise
603 proportionally to energy availability. However, due to the declining effect of prolactin on
604 insulin resistance, insulin rises more steeply and overshoots typical “post lactation”
605 levels (set at 1.0). Estradiol levels rise proportionally to insulin with a slight, arbitrary lag
606 time, while postpartum weight gain is proportional to the product of energy availability
607 and insulin. The resulting pattern is represented in Figure 6 with parameters adjusted to
608 be roughly equivalent to observations made on the Toba. Once again, variable values
609 are relative with 1.0 representing adult, non-lactating values of all variables except PRL,
610 where 1.0 represents peak values early in lactation.

611

612 The heuristic value of the mathematical model is to make explicit the fact that the
613 mutual interactions of a core set of hormones regulating energy allocation, interactions
614 that are well-established in the literature, are sufficient to generate the rather complex

615 trajectories of hormones and anabolic variables (e.g., growth rate, milk production,
616 weight gain) that are observed during two important life history transitions, puberty and
617 the post-partum resumption of ovarian function. It is not necessary to assume any
618 special set of interactions or drivers to generate these patterns. Rather the “switch”
619 from growth effort to reproductive effort is latently embedded in the effect these
620 important regulators have on each other. Natural selection has been able to leverage
621 the same endocrine architecture to orchestrate two different life history transitions by
622 making use of two different, but phylogenetically related, modifiers of anabolic energy
623 allocation, GH and PRL. Although beyond the scope of this paper, it can be argued that
624 this architecture has analogues in other vertebrates (Chandrashekar and Bartke, 2003,
625 Kawashima et al., 2007, Flatt and Heyland, 2011).

626

627

628 *Concluding comments*

629

630 The model framework presented here is just that: a model that represents only a
631 few of the major features of a complex network or interacting signals that govern human
632 energetic allocation. Its heuristic value is illustrated in its ability to capture the major
633 signals and interactions in sufficient detail to illuminate the dynamic aspects of the
634 control of energy allocation during major life history transitions. In doing so, it helps to
635 connect our knowledge of the mechanisms that govern energy allocation with the
636 predictions and tradeoffs that feature in life history theory. As a major branch of

637 evolutionary theory, life history theory has proven very powerful in predicting and
638 explaining major features of life history diversity, and in doing so it leans very heavily on
639 generalized concepts of energetic tradeoffs. But less effort has been made to integrate
640 life history theory with proximate mechanisms until recently (Flatt and Heyland, 2011).

641

642 The model presented here also underscores the central role of insulin, not as a
643 gluco-regulatory hormone, but as the major gatekeeper of energy allocation to mid- and
644 lower level physiological priorities. Insulin does not simply clear glucose from the
645 circulation to guard against negative effects of hyperglycemia, it directs energy toward
646 growth and reproductive effort, synchronizing investment in those physiological
647 categories with the availability of metabolic energy over and above the requirements of
648 higher priority categories. This centrality of insulin in the modulation of energy
649 allocation helps to make sense of the phylogenetically highly conserved relationship
650 between insulin and insulin-like signaling and lifespan variation (Barbieri et al., 2003;
651 Singleton, 2011; Tatar et al., 2003). Insulin is one of the best known and longest
652 studied human hormones. It may not have the cachet of more recently identified
653 neuropeptides and cytokines, nor does it represent control of the soma by the CNS. Yet
654 its role in life history energetics is crucial.

655

656 Finally, although developed in the context of human physiology, there is reason
657 to suspect that the framework presented here may have more general application,
658 either directly or as a template to modify and build on. The comparability of the

659 trajectory of C-peptide of insulin in relation to the postpartum resumption of ovarian
660 function in humans and chimpanzees is one example that supports this notion. The
661 framework developed and presented here may serve as an impetus for comparative
662 studies of the hormonal architecture of energy allocation in non-human primates and
663 mammals generally.

664

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896 **Figure Captions**

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899 Figure 1: The basic framework of energy flow underlying human life history energetics.

900 Numbers associated with the arrows refer to the groups of hormonal regulators

901 specified in Figure 2. The parenthetical number associated with energy flow from

902 available metabolic energy to activity indicates potentially weak or indirect hormonal

903 regulation.

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906 Figure 2: Categories of hormonal regulators associated with the pathways of energy

907 flow specified in Figure 1. Examples of major hormonal regulators in each category are

908 given and further elaborated upon in the text.

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911 Figure 3: Body composition changes (means \pm SE) in adolescent females in The

912 Gambia during periods of relative energy abundance (harvest season) and energy

913 constraint (hungry season) subdivided by growth rate. Details provided in Reiches et al.

914 2014.

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917 Figure 4: Trajectories of growth hormone, growth rate, estradiol, and insulin during
918 puberty generated by a simple model of the basic framework of human life history
919 energetics presented in this paper and illustrated in Figure 1. The Y-axis units are
920 expressed in proportion to adult values for each variable. Details of the model are
921 provided in Supplementary Materials.

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924 Figure 5: Plots of first morning urinary C-peptide of insulin levels expressed as a
925 proportion of individual, post-resumption average levels for each individual during the
926 postpartum lactation period as observed among Toba women compared with the
927 trajectories of (A) BMI and (B) urinary estrone conjugates (urinary metabolite of
928 estradiol). Compare these trajectories with those generated by the model depicted in
929 Figure 5. Data from Ellison and Valeggia 2003, Valeggia and Ellison 2001, 2003, 2004.

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932 Figure 6: Trajectories of insulin, estradiol, postpartum weight gain, energy availability,
933 and prolactin during the postpartum lactating period generated by a simple model of the
934 basic framework of human life history energetics presented in this paper and illustrated
935 in Figure 1. The Y-axis units are expressed in proportion to adult values for each
936 variable. Details of the model are provided in Supplementary Materials.

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