Chapter 6
of

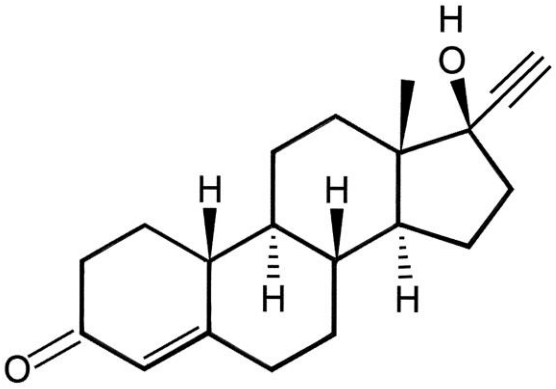
Contrary Life and Technical Fixes
from
malaria vaccine
to
hormone contraceptive

Alan R. Walker

Copyright: Alan R. Walker
Published 2015

alanrwalker books, Edinburgh
http//www.alanrwalker.com
ISBN: 0-9545173-2-6

Hormones, pregnancy and the Pill



At ten years old she had grown to thirty one kilos in weight – over the threshold for her natural surge of growth. She started to become aware of other changes in her body, she felt ungainly and sometimes uncertain of her mood. From now on she would be growing taller by nine centimeters each year until her transition through puberty was over, in four to five years. She was happy and well cared for in a family that ran a clothing business in Kumasi, Ghana. Her father ran the textile import side whilst her mother ran the garment workshop; all built up from her grandfather's tailoring shop. A strong family business, it traded in new lines of fashionable clothing, often using the traditional boldly patterned kente cloth. The girl, eldest amongst five siblings, was expected to learn then share her mother's business role once she had finished at secondary school.

In her brain a switch had changed, involving many tissues, many neural and biochemical pathways. The switch increased the concentrations of reproductive hormones circulating in her blood and diffusing from one tissue to another. The hormones signaled to ovaries, uterus and vagina to start their maturation to adult form and function. They also signaled the laying down of fatty tissue to mold her feminine shape. In a few years these hormonally coordinated developments would transform her from a girl to a person capable of bearing children; physically into a woman, if not socially ready for motherhood.

Her brain was the central source of these signals, but only a specialized part: the hypothalamus. This was the size of a bean, nestling below the main mass of her brain. Suspended by a thick stalk down from the hypothalamus was a similar sized pair of organs, the anterior and posterior pituitary glands (or adenohypophysis and neurohypophysis). Through the connecting stalk ran many neurons and blood vessels –

the pituitary glands and hypothalamus were in intimate physiological and neural contact with the main brain. Her hypothalamus linked her autonomic and centralized nervous system to her body's diffuse hormone system. Both hypothalamus and pituitary glands secreted hormones and these hormones in turn would stimulate other remote tissues to secrete hormones when needed. Her nervous system transmitted electrical signals along discrete fibers to specific cells to be activated. Her hormones, as her endocrine system, broadcast chemical signals.

Most of these separate chemical signals reached every cell in her body through the circulation of blood. But only a few types of cells would respond to each signal because only they carried the precise and specific receptor molecules for the signal. These receptors, as individual molecules, translated the relevant signal into the correct action of the cell: to grow, or to synthesize and secrete some other molecule. Thus the trillions of cells comprising her body were coordinated by signals broadcast to all of them.

To start this maturation through puberty, cells in her hypothalamus first synthesized then secreted a proteinaceous hormone, a neuropeptide called gonadotropin releasing hormone (or gonadotrophin . . .). This was secreted into a small portal vein that carried it directly down the connecting stalk to her anterior pituitary gland. There it encountered cells known generally as gonadotropes.

These are specialized for synthesizing hormones known as gonadotropins, the various hormones that support the maturation of gonads; in this case her ovaries. The gonadotropin releasing hormone binds, as a key in a lock, to its specific receptor molecule on the gonadotrope cells. Many millions of molecules of that one kind of hormone bind to millions of that one kind of receptor molecule. The receptors for these proteinaceous hormones are large, made of glycoprotein and adapted to sit astride the outer plasma membrane of the relevant cells. Each gonadotrope cell bears thousands of molecules of its relevant receptor.

The first of these gonadotropins to be stimulated was follicle stimulating hormone. So named after the structures in her ovaries that were supporting her supply of oocytes, or incubating her eggs in plain words. This hormone rose steadily in concentration during her passage through puberty.

Follicle stimulating hormone is a small molecule of glycoprotein, 28 kilodaltons molecular weight. It binds to a receptor molecule of 75 kDA that is itself coupled to G-protein sitting within the plasma membrane of the right kind of gonadotrope cell. Once a receptor molecule forms a complex with the hormone, as a key working in its lock, the combination starts a series of enzyme catalyzed reactions in the cytoplasm of the cell. These reactions control the required activity of the cell to grow then synthesize and secrete further reproductive hormones.

A closely related gonadotropin is luteinizing hormone, named after the special effect it has on the activity of one follicle that would become temporarily dominant in her ovaries. This glycoprotein hormone is also synthesized and secreted from the anterior pituitary gland. It works synergistically with follicle stimulating hormone to mature the ovaries, using similar receptors and reaction pathways.

By the time of the girl's spurt of growth another type of hormone was being produced from cells of her ovarian follicles. This hormone was estradiol (or oestradiol) the most important of a group called estrogens, after the estrus cycle of mammals. It would at this stage in the girl's development control much her maturation into a woman.

In contrast to the proteinaceous gonadotropic hormones this estradiol consists of a steroid molecule. Steroids are small molecules based on a skeleton of seventeen carbon atoms. These atoms occur in four rings bound in an angular row, three of the rings are six sided and one at the end is five sided. Bonded variously to this skeleton are more atoms: hydrogen, oxygen, carbon, or larger groups of these. The patterns of these atoms protruding from the skeleton define the character of each species of steroid; there are thousands of known species. Because steroids are readily soluble in lipids, they easily diffuse across the lipid based plasma membrane of cells, then across the cytoplasm to enter the nucleus. It is here that steroid hormones bind with their receptor molecules, if present in a particular type of cell. This binding activates, via steroid response elements and transcription factors, genes that are specific to the hormone. In turn the activated gene directs cytoplasmic structures of the cell to grow, or to synthesize other molecules for specific pathways of development.

Testosterone also circulated in her blood, influencing her sexual maturation. Her ovarian follicle cells synthesized this testosterone. The precursor they started with was cholesterol, an easily available steroid in her body. A chain of reactions in the cells passed the molecule through a series of alterations to the patterns of atoms and groups attached to the stable skeleton of carbon rings. The immediate precursor of testosterone in this chain of reactions was androstenedione. This molecule was converted directly into one of several estrogen hormones by action of aromatase enzyme. (Or estrogen synthetase, catalyst for aromatization. A carbon ring of a steroid could have an aromatized form like the fundamental six carbon ring of benzene, an aromatic hydrocarbon.)

Alternatively androstenedione could be converted directly to testosterone. From testosterone just one simple aromatization would produce estradiol; from cholesterol to estradiol by a chemistry kit of ingenious flexibility.

The ovarian follicles, busily producing hormones, surrounded her oocytes in a series of layers. The follicles were small and numerous in her ovaries as she entered

puberty. Each oocyte had been there since she was an embryo four weeks old. Female germ cells, called oogonia at this stage, had migrated away from the endodermal tissue that would later form her gut. The germ cells gathered with ordinary somatic cells to form a pair of primordial ovaries near her spine. In these minute ovaries her oogonia were replicating by ordinary mitotic cell division. Around the oogonia gathered somatic cells to become functional layers of the follicles. These follicular layers would later become factories for the production of reproductive hormones.

The germ cells were a genetic line passed from generation to generation: a germ-line. The girl had inherited the genetic constitution of these cells from her mother and father, and in turn her children would inherit them. They were the only line of cells kept immortal by being passed from person to person, the only cells capable of forming gametes and then fusing as a zygote that would then develop into a new human. Whilst she was still a young embryo her diploid oogonia, each with a full set of twenty three pairs of chromosomes, started to divide by a reduction division, by meiosis. They became primary oocytes. But they were only part way to becoming haploid gametes with only twenty three unpaired chromosomes. The meiosis proceeded only as far as the stage known as prophase. Then the primary oocytes became quiescent. Some of them would remain quiescent for decades.

When she was born each of her ovaries was packed with one million oocytes. After starting on the multi-stage division of meiosis there was no going back to replication by mitosis. Most of these oocytes were doomed to regress, die and be recycled within her ovaries. She would still have a total of forty thousand oocytes by the time she completed puberty but of these only four hundred would be likely to mature into a single egg each month, ready to be fertilized as she aged toward menopause.

When she reached a weight of forty seven kilos she passed the minimum at which she could possibly support the massive demands that any pregnancy that might now occur. She approached the end of puberty during her fourteenth year and by then her ovarian follicles were busy secreting estradiol. She began menstrual cycling; for her a twenty eight day interval. Each cycle started with the shedding of the inner lining of her uterus. This was the lining that had been capable of accepting and nurturing the beginnings of an embryo.

From her older friends at school she found the best advice about what was happening and how to manage the inconveniences, aches, and mood swings. She was determined not to let these changes interfere with her school work. Already she was aware of her talent at gaining good marks in most subjects. Could she be accepted into a college or university course, what subject might she be best at?

Yet another cycle started, a small bleed at the usual time, as her uterus spontaneously changed its structure. Her uterus was distinctly layered. Its outer bulk, the myometrium, was packed with powerful smooth muscles. Internal to this, facing the lumen, was the endometrium layer. The basal layer of the endometrium, next to the muscular layer, was richly supplied with a specialized blood supply and its tissues had a prodigious ability to support the regrowth of the innermost endometrial layer that would be shed during each cycle. This inner layer had a looser more spongy structure with large spaces filled with venous blood and a dense array of tubular uterine glands that opened into the cavity of the uterus. This would become the functional layer of a pregnancy; part of it would form her contribution to the placenta. Without a pregnancy this endometrial layer was completely shed as menses – the scraps of tissue and pools of blood – over the first five days or so of each cycle.

As the cycle progressed a cohort of twenty follicles was activated from the fixed stock in one of her ovaries. Her ovaries shared this repeated work between them, randomly. The follicles grew their layers and expanded. The outermost surface of each follicle was a basement membrane. Underneath this lay a thin membranous theca externa, then the fatter cells of the theca interna. Innermost was a thick layer of granulosa cells. The theca interna cells were supplied by a dense network of capillaries from the supporting tissues of the ovary, but the granulosa layers had no blood supply. At the center of a follicle nestled the single oocyte. As a follicle grew there developed a liquid filled space, the antrum, around the oocyte. The oocyte became suspended in this liquid by a thin stalk of cells called cumulus that also surrounded the oocyte.

Toward day seven of her cycle, follicle stimulating hormone was activated into secretion from her anterior pituitary gland by action of gonadotropin releasing hormone. Meanwhile the granulosa cells of her follicles had been producing more receptor molecules to this stimulating hormone. The granulosa cells grew by individual volume and number and started to secrete estradiol. This hormone diffused outward to the adjacent layer of theca interna cells. From there estradiol was carried into the blood circulation by the embedded capillaries. The basal layer of her endometrium responded to this rising concentration of estradiol by rejuvenating the inner functional layer.

At the same time luteinizing hormone circulating in her blood was increasing its concentration, as were its receptors. These receptors were confined to the theca interna cells at this stage of the cycle. Luteinizing hormone stimulated the conversion of androstenedione to testosterone in these theca cells. From them the testosterone diffused into the granulosa cells and in turn these cells aromatized testosterone into estradiol.

Of the cohort of developing follicles most of them regressed, they became atretic, and were recycled within the ovaries. By about day ten only several follicles

remained, expanding substantially in their volume. Within these large follicles the intense local increase in estradiol secretion stimulated the development of receptors for luteinizing hormone also on the granulosa cells, in addition to their presence on theca interna cells. This prepared these cells to respond to an impending surge of luteinizing hormone in several more days.

As the concentration of estradiol increased slowly it signaled to the hypothalamus to alter its secretion of gonadotropin releasing hormone such that the anterior pituitary gland was inhibited from secretion of follicle stimulating hormone. At this reduced level of follicle stimulating hormone only the follicle that bore the highest density of receptors for this hormone could continue to grow. That follicle, the dominant one of the active ovary, was destined to provide the single oocyte of that menstrual cycle. As the dominant follicle expanded to twenty millimeters in diameter it migrated toward the wall of its ovary. It arrived opposite to where the internal opening of an oviduct was itself aligning. As the follicle changed its position it also matured its receptivity to luteinizing hormone.

The growing dominant follicle produced so much estradiol that a threshold was reached. Beyond this, estradiol's inhibition of the production of gonadotropin hormones switched to stimulation. At days twelve to thirteen her anterior pituitary gland produced a surge of luteinizing hormone, together with a wave of follicle stimulating hormone. These emphatic signals started preparation for the next stage in the life of the dominant oocyte: ovulation. They also switched the granulosa cells of the dominant follicle over to a new capability: to synthesize the steroid hormone progesterone.

Approaching day fourteen of her cycle, the oocyte in the dominant follicle completed its first meiotic division. It became a secondary oocyte ready for discharge into the oviduct, ready to ovulate. As the wall of the follicle pressed against the wall of the ovary both ruptured. Liquid from the follicle's antrum flushed the oocyte out into the peritoneal cavity. A strange place to be – by a quirk of anatomy the open end of each oviduct is not connected to the ovary it serves. However, the fringed opening of the oviduct closed around and swept up the oocyte then pushed it deeper inside.

The meiotic divisions for this female germ cell had been asymmetric. Only one oocyte had developed from one oogonium instead of the potential four. Thus the single oocyte had grown large, potentially visible to unaided human vision. It would need all the cytoplasmic resources it could muster to cope with the tasks that lay ahead. As soon as the oocyte was within the duct it began its second meiotic division, proceeding as far as metaphase stage. In this way the oocyte became a female gamete. It was ready to be fertilized by a male gamete, as a spermatozoon that might be migrating up the oviduct. As long as there were some spermatozoa available.

The remains of the follicle had much work ahead, it needed to transform into another type of hormone factory. The ruptures in the walls of the follicle and ovary healed. The follicle retreated into the body of the ovary where it transformed into a large mass of cells called the corpus luteum. Its granulosa cells were now secreting much progesterone into the blood circulation. This rising concentration of progesterone acted on the hypothalamus to inhibit the secretion of gonadotropin releasing hormone. This in turn inhibited the gonadotrope cells in the anterior pituitary from their secretion of luteinizing hormone. A further steep reduction of luteinizing hormone came as the rising synthesis of progesterone in the corpus luteum supplanted the synthesis of estradiol. As estradiol declined it switched back to its former inhibition of synthesis of follicle stimulating and luteinizing hormones.

Following that switch after ovulation, both estradiol and progesterone would be present at slowly fluctuating concentrations in her blood. These two hormones were still needed to promote the final maturation of her endometrium. Its functional layer developed thickly with a specialized system of spiraled arteries and a dense array of uterine glands that opened into the cavity of the uterus. The endometrium readied itself for a pregnancy.

There were no spermatozoa available – none to swim up the lumen of her uterus and enter an oviduct to meet her oocyte that was slowly being pushed down her duct. Without a spermatozoon and fertilization the oocyte was fated to die and be flushed away.

The concentration of luteinizing hormone continued to decline to a low plateau by day twenty. If there had been a blastocyst starting to develop into an embryo there would soon have developed an alternative source of hormonal support for the corpus luteum. Without this stimulus the corpus withered into a residual body, the corpus albicans, that remained in the ovary. Thus the concentrations of both progesterone and estradiol declined after about day twenty two. Without support from these hormones the functional layer of the endometrium could no longer maintain its specialized structure and physiology. It responded with two days of ischemia, a closure of its blood supply. So this outer layer of her endometrium died from lack of fresh blood. It disintegrated, was shed and voided. Another cycle started.

♦

The young woman decided to try for a course in business studies, influenced by her memories of her parents worrying and arguing about the maze of contracts, permits, legalities they had to negotiate week by week. Maybe she could solve some of these problems, maybe help expand the family business. She spent four years at the School

of Business Studies, on the Legon campus of the University of Ghana in Accra. In her final year she fell in love with a student of agricultural economics. Finding any privacy in the bustling campus, in Accra, or back home in Kumasi was difficult. When they could make love she used a diaphragm, tried and gave up using a coil; sometimes he used condoms. Variously, and always with that background worry – are we being sufficiently cautious?

Now in her late twenties, she at last gained sufficient professional reputation and her husband worked for Ghana National Agricultural Export offices in Accra. Time to start a family – she found a new part-time post with another firm. Wife and husband had grown in their passion for each other; young, fit and content with family life. They looked forward to making love without the distraction of diaphragms or condoms for a while. They each had varying levels of three other potent reproductive hormones circulating in their blood. They often made love, their desire for each other enhanced by their testosterone. Another hormone called oxytocin, released from the posterior pituitary gland, heightened their tactile pleasures of cuddling and stroking. Then after their orgasms prolactin hormone, secreted from their anterior pituitary glands, gratified and relaxed them.

Another cycle started. The basal layer of her endometrium, with its intact tissues and blood supply, recovered and again grew a functional layer by day five. With no more progesterone and estradiol being produced from any active corpus luteum, her hypothalamus was free to produce a surge of gonadotropin releasing hormone. In response, follicle stimulating hormone again rose in concentration. By day fourteen of this new cycle a dominant follicle ovulated.

At a climax of their lovemaking, her husband ejaculated five milliliters of semen around her cervix. Five hundred million spermatozoa lashing with their long tails swam through the seminal liquid and vaginal mucus. Most of the ejaculate leaked away, nevertheless thousands of spermatozoa penetrated the opening of her cervix. Here they found more watery mucus through which they swam up her uterus. Eventually two hundred of them entered each oviduct and struggled onward toward a potential oocyte. These survivors had transformed since they left their testes. A multitude of biochemical processes gave them a new physical and metabolic character in a process called capacitation. They were ready for their singular task.

Simultaneously her new oocyte had survived its tricky passage from ovary to oviduct. The delicate fimbriae, along with the cilia and smooth muscles of the duct, harvested their cargo and squeezed it down past complex epithelial folds. This epithelium was secreting watery mucus rich in nutrients that supported both oocyte and spermatozoa. Neither oocyte nor spermatozoon had long to live in the vulnerable states

they were in. To be in the right place at the right time would be a tight coincidence: ten or so millimeters in the duct, and a day or so either side of ovulation.

The few surviving spermatozoa swarmed over the oocyte. A thin layer of loose cumulus cells and the non-cellular zona pellucida covered the cell. These would be the final barrier for the spermatozoa, only one of which should be allowed in. At the instant of penetration by that spermatozoon the oocyte switched off its receptivity. The entering spermatozoon triggered the oocyte to complete its second meiotic division and become a single haploid female gamete. Soon fusion of the nuclei of the female and male gametes, known as syngamy, created a diploid zygote cell.

By chance of meiotic shuffling of chromosomes the fertilizing spermatozoon's single sex chromosome was a Y for maleness, rather than X for femaleness. The female gamete could only have one of her two X chromosomes. So the zygote, with its full set of twenty three pairs of chromosomes had an XY pair of sex chromosomes. The zygote was male. This single cell would divide again and again to make a man of trillions of cells. He would be unique amongst all humans due to the mixing and crossing over of genetic elements during meiotic divisions of his parent's germ cells.

This is what all this complex and messy business of sexual reproduction was for: to produce genetically unique offspring. Newly unique individuals of the species might have the capacity to respond a fraction better to new threats from competitors, pathogens, parasites, predators, or a changing environment. And so survive better to pass on that genetic advantage down the germ line of their offspring.

The zygote divided by ordinary mitotic cell division, then another and so on to quick succession. By the seventh round of divisions the blastocyst grew as a hollow ball. This ball was the same volume as the oocyte it had developed from – the dividing cells had halved in volume each time. This potential new human now faced its first crisis. To develop any further, to live longer than the many oocytes that had passed this way before, this blastocyst had to latch onto its mother. It needed to burrow and implant within the tissues of her uterus.

On the fifth day after fertilization the oviduct pushed the blastocyst through its narrow opening, its isthmus, into the uterus. Passage was aided by the relaxing effects of progesterone on the smooth muscles of the isthmic sphincter. Before the blastocyst could implant it needed to reveal its cellular surface and character. These were still covered by the zona pellucida, but by secreting digestive enzymes the blastocyst hatched out of this capsule. Now this new organism was as naked and vulnerable as it could be, desperate for its mother. Vital to survival were the molecules protruding from its outer cell plasma membranes. These had to interact with the molecules similarly protruding from the plasma membranes of the epithelium of its mother's endometrium. The endometrial cells had been prepared by the estradiol still being secreted by the

mother's corpus luteum. These cells grew dense brushes of microvilli to increase both their surface area and number of molecular receptors. They made ready to bond with the blastocyst.

Cells of the blastocyst continued to divide rapidly and create an asymmetric ball shape with one pole containing a thick inner mass at its wall. This mass was the embryoblast, the potential embryo. At this pole the blastocyst first touched the endometrium. The microvilli on the cell surfaces of both bodies meshed together. Contact! the signal shouted at the mother's brain. Her hypothalamus switched off its pulsing signals of gonadotropin releasing hormone so that her menstrual cycle would stop then convert to the new regime of pregnancy.

The outer layer of the blastocyst developed into a layer of cells dedicated to feeding the embryoblast. This new layer was the trophoblast. These two blastoid tissues formed the conceptus, a combination of what would soon become the embryo together with all its enveloping supportive membranes. Cells of the young trophoblast individually pushed their way between the epithelial cells of the endometrium. This invasion switched on a reaction, the decidual reaction, in the underlying tissue of the endometrium such that it lost its structural integrity. The disintegrating cells provided nutrients for the blastocyst.

As this invasion proceeded the trophoblast cells lost their individual identities and fused into a syncytium, a mass of cytoplasm containing many free nuclei. This new tissue, the syncytiotrophoblast, grew as the conceptus burrowed below the endometrial surface. By the tenth day after fertilization the implanting conceptus had grown its syncytiotrophoblast into a spongy structure. The contents of the uterine glands of the endometrium flowed into the spaces of this sponge to be digested as nutrients. With this new source of food in the form of its mother's cells and tissues the embryoblast quickened its development. As early as day twelve the first sign of a proper embryo appeared: a crucial folding of tissue to form its primitive streak which defining the alignment of the spine.

The conceptus had a different genetic constitution from its mother: half its genes were from its father. Thus it appeared to the immune system of its mother as not of herself. It appeared foreign. The part of her immune system controlled by the genes of her major histocompatibility complex automatically recognized anything that was not of herself. Anything that was non-self was to be treated and dealt with as a threat to health and life. The mother was in danger of reacting to her conceptus as a pathogenic object, to be killed and removed. Somehow the conceptus managed to present a bland immunological character to her immune system. She would not reject it, but their relationship would continue in a complexly delicate state of immunological truce until after the birth.

Not only did the syncytiotrophoblast start to develop as part of the placenta, it started to synthesize and secrete another hormone. Chorionic gonadotropin, named after a major membrane of the conceptus, would replace the role of the rapidly declining luteinizing hormone. By stimulating the mother's still active corpus luteum a continuing supply of progesterone and estradiol would be provided for the earliest stages of pregnancy. These two hormones would be needed increasingly to support the growth of the placenta.

Day twenty two post-fertilization saw the first beats of the embryo's heart. By day twenty eight, at no more that four millimeters long, it was already recognizable as a vertebrate animal. All the primordia of its organs were in place. Of the placenta all the major contributions of the conceptus were formed and active. A layer of the blastocyst that had formed at the same time as the syncytiotrophoblast was now well developed. This was the cytotrophoblast, composed of individual and coordinated cells. This layer expanded out from the blastocyst toward the syncytiotrophoblast. As it did so it developed villi protruding into the tissue of the endometrium that the syncytiotrophoblast had prepared. These villi were the primordia of the chorion membrane of the embryo that would become the embryo's part of the placenta.

Eventually the chorion would form a disc shaped plate, interdigitating over a large area with the mother's uterine contribution to the placenta. The highly developed arterial and venous blood vessels of her endometrium would convert into an open low pressure supply of her blood, bringing oxygen and nutrients whilst removing wastes. The mother's blood supply was separate from the embryo's blood circulation. Small molecules easily diffused from her blood across the thin layer of syncytiotrophoblast and through the single cell thickness of the embryo's capillaries. The area over which these transfers could occur became huge as the chorionic villi grew like leaves on a tree.

Between days fifty to sixty three the embryo gained its human features, although only thirty millimeters long. The embryo became a fetus. It had lost obvious signs of a tail; grown clearly jointed limbs complete with separate digits; developed a large domed head complete with rudimentary eyes, ears, nose and mouth. All this was attached to its mother by a massive umbilical cord and placenta. This fetus now had much to accomplish, in a compromised physiological alliance with its mother. More hormones were needed to coordinate this relationship.

As the embryo's part of the placenta grew it continued to secrete sufficient chorionic gonadotropin to stimulate the mother's corpus luteum. This in turn secreted rising quantities of progesterone and estradiol. But by fifty days of the embryo's growth, secretion of chorionic gonadotropin had declined. As the role of the mother's

corpus luteum was supplanted by the syncytiotrophoblast it regressed into another corpus albicans.

The placental syncytiotrophoblast started to synthesize and secrete both progesterone and estrogens. The estradiol of the corpus luteum was replaced by the closely related but weaker hormones estriol and estrone. These continued the work of maintaining the vigor of the placenta and increasingly the development of the mother's mammary glands in early preparation for secreting milk.

The mother made her own contributions. Her anterior pituitary gland was secreting more and more of the hormone prolactin. The prolactin circulating in higher concentrations started to develop the ability of the lactiferous cells in her mammary glands to actually synthesize milk.

The rapidly growing fetus needed ever greater supplies of nutrients. These could have been coming from a mother who was short of food herself. Not the case with this well nourished pregnancy; nevertheless the embryo's syncytiotrophoblast had started, about day fifty, to produce the polypeptide hormone called placental lactogen. As this rose in concentration it manipulated the mother's metabolic rate, acting like a growth hormone, in favor of diverting nutrients to the fetus. Even in times of lean seasons and little food to gather, the biological priority was to support the fetus.

Mother and son had much work to accomplish. Both within tightly coordinated timetables set automatically in their separate central nervous systems. Eventually, at two hundred and sixty days her son prepared for birth. He oriented correctly – head first toward his mother's cervix and pelvic girdle. It was going to be a tight fit. A large head adapted for the human specialty of high intelligence was up against a pelvis adapted for the human specialty of walking upright on two legs. Help from more hormones would soon be needed.

As the pressure in her uterus increased the walls of the inner end of the cervix were stretched. The stretching directly stimulated sensory nerves and impulses travelled across to her spinal cord. Here the impulses crossed synapses to nerves leading up her brainstem and into the hypothalamus. Many more nerve connections down to the posterior pituitary gland were stimulated and from this gland strong pulses of oxytocin were released into the blood stream. By this stage of pregnancy the numbers of receptors for oxytocin in the myometrial muscles of the uterus had increased greatly. Binding of hormone and receptor stimulated contractions of the uterus. Contractions increased the pressure on the cervix, and so more oxytocin was produced. The contractions came in waves of ever increasing strength as this positive feedback loop (Ferguson reflex) acted on her uterus, striving to push the baby out.

She was in a maternity ward of the Korle Bu Teaching Hospital, central Accra. After the end of her third stage of labor her baby was at last resting on her chest. The

midwife had made the basic checks on his condition whilst a nurse clamped and cut his umbilical cord. Their joint placenta, closest possible physical bond they would ever have, had been pulled away from the basal layer of the uterine endometrium by tension from the baby's umbilical cord. It emerged as a bloody disc the area and thickness of the mother's hand – its multiple tasks all complete.

Soon after delivery more oxytocin played another role: it promoted mutual bonding of mother and baby as they cuddled close, skin to skin for thirty minutes before he was away for a full wash and more detailed checks of his health. That chemically mediated bonding would be reinforced for the rest of their separate lives. From breastfeeding through to the simplicity of cuddling, a warm hug, a touch on the shoulder or even a smile that might suffice. Social and tactile primates, hormonal mediation, humans naturally looking out for each other.

Her own prolactin continued to circulate ready to stimulate the actual synthesis of milk. After birth the concentration of prolactin fell steeply but then stabilized at a lower level. This new status was maintained by a reflex that started with the baby's first feed. His hunger drove him to both suck at a nipple whilst squeezing it between tongue and hard palate. These pressures set off nerve impulses to his mother's spinal cord, to connect to other nerves going to her anterior pituitary where synthesis of prolactin was induced: the suckling reflex. The pulse of prolactin stimulated receptors on mammary cells to synthesize and secrete more milk into the wide lactiferous ducts and sinuses. Her glands temporarily stored this milk ready for the next feed, for release when again stimulated by oxytocin as she lifted her soft warm baby to a breast. This was another reflex, milk ejection or let-down; so strong that the sound of another baby crying would sometimes trigger a spurt of milk into her clothes.

She intended to breastfeed him fully for at least six months. So the prolactin that was repeatedly stimulated by his suckling continued at its average steady level. This hormone suppressed any tendency for secretion of gonadotropin releasing hormone to restart. Without this releasing hormone there would be none of the cascade of hormones that would start another menstrual cycle. Her baby's suckling suppressed her ovaries and stopped her menstruation, a lactational amenorrhea. She knew, however, of how early cycles can re-start in some women; so back on with the barrier contraceptives for the couple.

Their son weaned easily. By seven months the first signs of return of menstrual cycling came as her prolactin level dropped below the threshold for suppressing gonadotropin releasing hormone. She returned to the family planning clinic of the maternity hospital to collect her pre-arranged first pack of combined oral contraceptive pills. She allowed herself to dream of a return to Kumasi to set up a larger home there,

to rear her child and maybe more, amongst her wider family and in fresher air and more space than could be had in the capital city.

♦

The evolutionary history of hormones can be traced back to at least the origin of multicellular life. Simple molecules, the steroids in particular, were used as signals in both plants and animals, and one hormonal molecule could serve many functions. The nature of reproductive hormones within the vertebrates shows distinct similarities from the simplest animals, such as *Amphioxus* lancelets, through to mammals.

Hormonal signals are analogue in nature, they vary continuously in timing and concentration, rather than being on or off as with digital signals. Signaling works with molecules transported, by diffusion or in the blood, to remote receptors specific to particular cells and organs. The variation of the multiple and overlapping signals, sometimes with negative and positive feedback loops, synchronize the activity of the body through time. Hormones work autonomously, continuously in the background. They work with delicately graded potencies and links to the genome. But whilst hormones interact closely with the nervous system and some are produced by the system, in no way can a nervous system do the job of a hormonal system.

The contrariness in this story does not lie not within the great complexity of hormones that this story of reproduction has revealed. When working normally, without genetic error, they coordinate the work of trillions of cells, of thousands of biochemical pathways and tens of tissues and organs that comprise multicellular organisms. Hormones are an awesome example of the beauty of how life works. The complexity of hormone interactions is a sign not of weakness or contrary design, but just the sign of a system that developed by natural selection of what worked best with the biological materials to hand. The contrariness of nature that is most important for this story lies elsewhere: in people's minds.

♦ ♦ ♦

At the University of Innsbruck, in Austria during the 1920s, worked a biologist called Ludwig Haberlandt. He invented the first hormonal contraceptive. By the 1930s the pharmaceutical company Gedeon Richter of Budapest, Hungary, was manufacturing this preparation and selling it to physicians under the brand name Infecundin. This drug had little impact at that time and it was not until the 1960s in America that the first effective hormonal contraceptive was manufactured and sold. Women had wanted a better contraceptive long before Ludwig Haberlandt's investigations and invention.

Their needs and demand drove the fierce social, political and legal battles growing from the 1900s in America, Europe and elsewhere. The story of how Haberlandt's well developed concept of hormonal contraception finally became realized as a packet of pills next to a woman's toothbrush as part of her daily routine starts with the discovery of the hormone produced by the corpus luteum of mammals.

Haberlandt did not know that this hormone was the active ingredient in his extracts of ovaries. Rather, four teams of researchers competed simultaneously during early 1930s to characterize it. The first to publish their results were George W. Corner and Willard M. Allen, at the medical school of the University of Rochester, New York State. They named this hormone from the corpus luteum as progesterone – a hormone for gestation.

A market for progesterone developed rapidly. Simultaneously a parallel market for estrogenic hormones and testosterone developed once their potent influences on metabolism and reproduction were better known. To produce these hormones in those early days required huge initial quantities of natural materials, which yielded minute amounts of hormone pure enough for use when injected into people. Edward Doisy, first co-discoverer of an estrogen, started with the ovaries of eighty thousand sows to extract 0.012mg of estradiol. For testosterone the testes of bulls were harvested from slaughterhouses by the tonne. Bulls are few in livestock rearing and their working testes are greatly valued by cattle farmers.

Extracts of reproductive hormones were very expensive – nevertheless highly demanded by patients and their clinicians. Organic chemists sought alternative sources. They knew that steroids are common in plants and they were confident of their ability to manipulate such steroids. They planned to synthesize new steroids from extracts of common plants to sell valuable hormones made from cheap sources.

Few chemists were more confident than Russell E. Marker of Laboratorios Syntex S.A., in Mexico City. Marker worked on the hunch that Mexican yam plants would be a more prolific source of starting steroids than the lily plants he had used when working at Pennsylvania State College in the early 1940s. These plants contained soapy molecules as steroidal saponins. His business proposition was to outcompete the cartel of American and European hormone suppliers by applying his newly invented chemical wizardry. This invention would become known as the Marker degradation; it transformed the saponin side chain protruding from the basic steroid skeleton. He used a progression of five steps, simple but closely controlled for speed of reaction, to convert the steroid known as diosgenin into progesterone.

The species of yams, *Dioscera composita* and *D. mexicana* are perennial leafy liana plants with a large, partly underground, tuber. They are inedible because of their bitter saponins, and unwanted until Marker explored botanically suitable areas of

Mexico paying bemused farmers to find and harvest these tubers. Soon Syntex could deeply undercut their competitors in the international trade for progesterone. They company was poised to expand and diversify.

Marker fell out with his partners at Syntex and in another of his individualistic moves set up an alternative company. To replace him the managers of Syntex hired George Rosenkranz, a refugee from war ravaged Europe looking for a job. Not just a skilled chemist but also an inspired manager, Rosenkranz built a team to exploit these yams for manufacture of a range of hormones. Enough was then understood of the chemistry of steroids to trust that the flexibility of transformations within these molecules permitted better derivatives of plant hormones for use in humans.

Cortisone was an obvious objective. It had been discovered several years after progesterone, and Merck & Co. in America synthesized it using a chain of thirty six difficult transformations starting with the bile acids from the gall bladders of slaughterhouse cattle. Selling at $US200 per gram in 1944 and greatly demanded as a relief from the pain of rheumatoid arthritis, cortisone excited the imagination of Rosenkranz. Could he devise a Marker degradation from diosgenin to cortisone? Could little Syntex undercut the big boys north of the border and over the Atlantic?

Rosenkranz needed a specialist. In 1949 he persuaded Carl Djerassi to leave his secure post at the New Jersey branch of the Swiss pharmaceutical company CIBA. Djerassi had worked there for four years after gaining a doctorate degree in steroid chemistry from the University of Wisconsin. He was keen to return to these intriguing molecules and was charmed by Rosenkranz with the promise of operational autonomy, good resources and shares in Syntex. Furthermore, Rosenkranz assured Djerassi he would have complete freedom to publish in academic journals. Syntex would develop an internationally exceptional record for publications relative to its minute size in those early days.

They recruited a team who after months of hectic work found themselves headlined in the weekly newspapers *Life* and *Newsweek* of 1951. Syntex won the race with Harvard University and Merck & Co. to partially synthesize cortisone. From yams! A publicity photograph shows Syntex researchers in freshly laundered lab coats and neatly groomed hair, all staring obediently at an enormous tuber squatting on a bench in front of George Rosenkranz. Of the full team the photograph shows: Alex Nussbaum, Mercedes Velasco, Gilbert Stork, Jan Pataki, Enrique Batres, Juan Berlin, Carl Djerassi, Rosa Yashin, Octavio Mancera and Jesus Romo. Industrial and academic chemistry was just developing in Mexico in those days but Syntex's company ethos attracted talent sufficient for their ambitions.

Invigorated by their success with cortisone Rosenkranz and Djerassi established a team to return to progesterone. They were stimulated in part by a

mysterious order from an American pharmaceutical company for a huge amount of progesterone. What clever trick of steroid chemistry might this company be planning? Furthermore, the conventional progesterone administered by clinicians to alleviate or cure problems with menstruation and prevent miscarriages, needed repeated administration by injection. The natural hormone has a half-life of several minutes in the body and does not survive even the earliest stages of digestion if administered orally. Many pharmaceutical companies sought various versions of progesterone that could be administered as a long acting depot injection or taken by mouth.

Djerassi gained confidence from a paper published in 1939 by Hans H. Inhoffen who worked for Schering AG in Berlin. The chemists there had invented and patented a method to synthesize partially a form of estrogen known as ethisterone for the gynecological market. This hormone also showed progestational properties. It had been manufactured and sold in Germany as Proluton C and in America as Pranone.

A crucial step of Inhoffen and his co-workers in Berlin was bonding a molecule of acetylene to the carbon atom 17 of the steroid skeleton on testosterone. The acetylene moiety projected like an arm from the only ring of the skeleton with five carbon atoms. Pure acetylene is a flammable gas common as a building block for industrial organic chemistry. Testosterone was thus converted into an estrogenic hormone that also had some properties of natural progesterone. Such is the flexible chemistry of steroids.

The Syntex team also had faith that another synthesis method, invented by Maximilian Ehrenstein and Willard Allen at the University of Pennsylvania in 1944, revealed how a partially synthesized form of progesterone called 19-norprogesterone, could be biologically active. Such progesterones, synthesized in a laboratory, became classed as progestins.

At Syntex the team combined their method for transforming diosgenin from yams into a progestin using a process called de-aromatisation that Arthur J. Birch had invented in Australia in 1950. Further manipulations bonded an acetylene to carbon 17. The final step to Syntex's new progestin came in 1951. An undergraduate student, Luis E. Miramontes, working there for his thesis, transformed the acetylated steroid into a molecule known to chemists as 19-nor-17α-ethynyltestosterone, and generically known as norethisterone. The team spent six months on this project.

Promptly they sent a sample to a biological assay laboratory in America. The lab reported that not only was this progestin substantially more potent than any other progestin or natural progesterone, but retained its potency when administered orally. Syntex applied for a patent, assigned to them, and written by Djerassi, Miramontes and Rosenkranz. Eventually this proved to be a highly profitable patent for Syntex and good fortune for anyone who had taken their early share options in the company. As

had Carl Djerassi, who retired a multi-millionaire to become a writer and patron of artists.

However, already there was a similar patent, granted in 1953 and assigned to G.D. Searle & Co. of Chicago. It had been written by Frank B. Colton for a progestin closely similar in structure and properties to the progestin from Syntex. Bryon Riegal at Searle had started a program to exploit the potential of improved methods of manipulating steroids. He learnt these methods working in endocrinology at the Mayo Clinic, where the anti-inflammatory properties of cortisone had been discovered. Riegal and Colton sought a progestin that would be easy for partial synthesis, potent and orally effective. From the long established firm of Searle, the better presented patent application, submitted later than that of Syntex, had been approved first. Their molecule was generically named norethynodrel.

The Food and Drug Administration of the USA separately registered both norethisterone and norethynodrel in 1957 for medical use. Both applications had sought only registration for the conventional use of progesterone-like hormones: regulation of menstruation and prevention of miscarriages. Both registrations proceeded rapidly through the registration scrutiny because, prior to 1952, the requirements emphasized medical efficacy rather than safety from harmful side-effects. Medical use of preparations of progestational hormones was by then well established and uncontroversial. Clinicians using them would have been aware of the potential of these drugs as contraceptives. That had been demonstrated experimentally as early as 1937 by A.W. Makepeace and colleagues at the School of Medicine in the University of Pennsylvania. They had proved that progestins can stop ovulation. Biologists and clinicians understood that women naturally produce two hormones that in one sense are contraceptive: estradiol and progesterone. But few of them were thinking in terms of a contraceptive made of a hormone, at least not as a product that could be advertised and sold as such.

♦

Birth control campaigners like Margaret H. Sanger thought daily about contraception. Thoughts yes, but only carefully guarded words on the subject did they dare say in public. Sanger had opened the first clinic to provide advice about birth control in the Brooklyn district of New York City, in 1916. Nine days after the opening police officers raided the clinic to arrest and charge Sanger. She broke her bail conditions by distributing more information, which led to a sentence of thirty days in jail. After several lengthy appeals a judge ruled in her favor and issued a ruling that doctors were legally permitted to prescribe materials for contraception. The police were just doing

their job: to enforce the Comstock Laws that the state of New York had passed decades ago. Newspapers eagerly covered this spicy story.

Anthony Comstock founded in 1873 the New York Society for the Suppression of Vice. In the same year he was the main proponent of a federal act of law passed by the US Congress for: 'Suppression of Trade in, and circulation of, Obscene Literature and Articles of Immoral Use'. Separate states passed similar Comstock laws, until at least forty five states of the union had such laws on their statute books. Literature on birth control, diaphragms, condoms and so on were deemed obscene and immoral. Some states had laws with sentences of years in prison. Edward Bliss Foote was a medical doctor who ran a clinic and provided advice and methods for contraception. He was arrested under a Comstock law in 1876, after being entrapped. On conviction he was fined $3,000.

Margaret Sanger's mother had been pregnant eighteen times over a twenty two year span, resulting in eleven live births. Margaret trained as a nurse and served people in impoverished districts of New York City. Her background and experiences of the lack of birth control information and means, combined with the spreading ideals of rights for women, forged her into a lifelong pamphleteer and activist for birth control. She expanded her ideas of what might be possible from political radicals in the city, including the social reformer and anarcho-syndicalist Emma Goldman, and the suffragette and pacifist Mary C.W. Dennett.

Sanger's second husband, a wealthy industrialist, was besotted by her vivacity and allure. Despite his conventional opinions and habits he supported her with the freedom and money to continue her battles. She would need every support for an enduring struggle resembling the Greek myth of Sisyphus, who was condemned to heave a massive boulder up a mountain only to lose grip every time nearing the top.

The campaigners for birth-control rights discovered the tactic of greatest potency was carefully managed challenges to Comstock laws. When lower courts ruled against birth-control the campaigners increasingly could find intellectual, legal and financial backing for appeals to higher courts. All the while this activity was good material for journalists and the proprietors of newspapers.

In 1932 Sanger arranged a delivery of diaphragms, pessaries, from Japan to a doctor in New York. Customs officials duly confiscated these potentially illegal devices. Sanger duly organized a lawsuit to contest this definition of illegal. By 1936 a federal court ruled on the case of *United States v. One Package of Japanese Pessaries*. The judge deemed the federal government to have no business preventing doctors from prescribing contraceptives to their clients. Birth-control became more newsworthy, more clinics opened across the nation.

Men who returned to America from the two world wars were familiar with condoms; their military commanders had taught the dangers of venereal diseases. The men's need and demand when they returned home massively increased the under-the-counter market in condoms. But Sanger was one of the many women who did not trust men to be in charge of contraception. Moreover, after the huge losses in those wars, followed by the cold war developing in the late 1940s, a national mood arose: more babies needed not fewer. For women wanting a family they could enjoy and nurture well, diaphragms and coils could be obtained but were difficult to find and fit and use effectively. Sanger dreamed of something like a normal medicine, in the hands of women and highly reliable.

Still campaigning intensely despite the frailty of her later years, Margaret Sanger met in 1950 a biologist who specialized in the physiology of reproduction. They were introduced by the medical director of the Planned Parenthood Federation of America, an organization that developed from an earlier version Sanger first established. The biologist was Gregory G. Pincus. Seven years previously Pincus and Hudson Hoagland, former colleagues at Harvard University, had created the Worcester Foundation for Experimental Biology. Named after a town in the state of Massachusetts, it was a fifty minute drive west from Boston. Fully private and independent, the laboratory relied on donors for basic research and contracts for biological assay of pharmaceutical samples. Pincus had turned increasingly to endocrinology and was soliciting materials to examine for progestational activity. Soon he was to receive samples of norethisterone from Syntex and norethynodrel from Searle.

By the 1950s Sanger and the steadily growing number of campaigners for women's reproductive rights had progressed far from their early days of the first birth control clinics and threats of arrest or worse. The annual conference that she organized could boast by 1925 of one thousand delegates from around the world; doctors, scientists, philosophers, political activists. Sanger was now financially able to put small funds into the Worcester Foundation, through Planned Parenthood, for progestational hormone testing. Thanks to the pragmatic genius of the biologist leading and performing much of the testing, Min Chueh Chang, the research could at least start.

The boldly named Foundation was housed in a dilapidated former residential building, hastily converted to its new role. Chang and colleagues improvised and penny-pinched, they jerry rigged their own apparatus and worked excessive hours for small salaries. The ethos was good, and Chang was never happier than at his lab bench. By 1953 the team had evaluated in rats and rabbits the effects of two hundred samples of various progestins. What was their influence on ovulation? They rapidly proved

fifteen of them to have efficacy in preventing ovulation and two of the best were norethisterone and norethynodrel.

Funding for this research in Worcester improved greatly from 1953 when Sanger introduced to Pincus one of her allies from her early days of the suffragette movement. Katharine Dexter McCormick had smuggled diaphragms from Europe into the early birth control clinics. She was the sort of lady imperious enough to get away such unconventionality. Tall, handsomely dignified, independently wealthy and with a degree in biology from the Massachusetts Institute of Technology, she then inherited another fortune when her husband died. He had suffered many years of schizophrenia and McCormick had established the Neuroendocrine Research Foundation at Harvard University in the hope of a hormonal therapy for such maladies. McCormick was pleased to donate to Pincus's exciting new development in hormone research. Possibly he could develop not just a fully effective contraceptive at last under women's control, but also in the form of a pill discreetly separate from love making.

Katharine McCormick continued to finance this laboratory research on contraceptives and continued through to the clinical and field trials. Much of this work would be done in the state of Massachusetts. Here the Comstock laws were of the strictest type, with harsh penalties continuing valid on the statute books into the1960s.

Gregory Pincus understood well the reputational, legal and political hazards he was leading the Foundation, his colleagues and supporters into. His early research on in-vitro fertilization at Harvard had attracted alarmist bad publicity and contributed to loss of his post there. Latterly he had regained his reputation by becoming the leading organizer of an annual conference for endocrinologists. He had been on friendly terms since Harvard days with a doctor likely to help extend the lab research into clinics.

John Rock was an obstetrician and gynecologist with a post at Harvard and a clinic in the Free Hospital for Women, in Boston. His specialty was helping infertile women become pregnant. He administered progestational and estrogenic preparations to manipulate the cycling of their ovaries and uteri. His strong religious convictions also inspired his promotion of the rhythm method for birth control. But by the time Pincus, Sanger and McCormick needed his help Rock had become convinced that effective hormonal contraception was the way to progress. John Rock was everyone's idea of the well established, well qualified clinician. Also he was conventionally handsome, in contrast to the boffin's aura of Gregory Pincus.

Rock's network of clinicians and endocrinologists was wide and he had good assistants. Miriam Menkin was a reproductive physiologist with experience of research in Pincus's labs. She did both the bench testing for Rock on this new project as well as the day to day supervision of clinical trials. Of Rock's physician colleagues the crucial one proved to be Celso Ramon Garcia. He led the start of clinical trials of progestin

from a project at the medical school of Puerto Rico. That country had since 1937 rescinded its laws against contraception.

Small scale trials on women volunteers also were being run by the mid 1950s at the Worcester Foundation, and also in Los Angeles under the leadership of Edward T. Tyler. Rock used a regime of progestin for a three month trial of daily doses for twenty one days of each month on volunteers from his clinic. The twenty one days per month schedule was copied from his often successful treatments to make women pregnant. He had used injections of progestational hormone to induce a false pregnancy that somehow reset the coordination between ovaries and uterus.

The clinical testers in Puerto Rico faced a daunting prospect. Nothing like this new contraceptive, now as pills in a small brown medicine bottle, had ever been submitted to the Food and Drug Administration or the medical establishment or the newspaper reading public. And contraception was still illegal in much of America. The pharmaceutical companies involved, Searle & Co. foremost, but also Parke Davis acting for Syntex, the American branch of Pfizer, and others, feared for their reputations over such a controversial product. Of the male managers struggling to make these decisions some were reluctant to believe that women would be prepared to dose themselves with this pill day by day, year by year. What dangers might appear in the long future? Was there a sufficient market for these pills?

A doctor from Detroit escaped her unhappy family life into a job with the Department of Public Health in San Juan, capital of Puerto Rico. She was another forceful activist with a mission: Edris Rice-Wray, always fashionably dressed, always working at a way through the many frustrations of public health medicine. By the time of the trials she was medical director of Puerto Rico's Family Planning Association and ideally connected for the project. Around the capital city were many districts where people were living in poor conditions and married women also burdened with lack of control over their wombs. They went through serial pregnancies and aged prematurely. They wanted contraception and wanted it under their own control: they became eager volunteers.

The practical problems were complex and varied. The pills, as a three week supply in a bottle were sometimes taken only after intercourse, or erratically when remembered in hectic lives. There were complaints of tender breasts, nausea, and menstrual changes. Language, educational and cultural barriers caused multiple confusions. Nevertheless the little round *píldoras* worked. Word spread, more volunteers enrolled.

Trials continued to Haiti, and in America the early trials expanded particularly in Los Angeles with Edward Tyler. By 1965 the directors of G.D. Searle & Co. gained confidence to apply to the FDA for registration of norethynodrel. By then this

progestin was formulated with a small proportion of an estrogen, mestranol, to consolidate the effect. They applied for clinical use in the familiar role of treatments for menstrual and miscarriage problems. The application was scrutinized intensely. Would these factory-made hormones cause infertility when no longer required by a woman? Would they damage her uterus? Were they a potential carcinogen? What about the risk of blood clots?

The FDA approved norethynodrel in 1957. Searle branded the pills as Enovid; it was the first combined oral contraceptive. In the next two years half a million women in America swallowed Enovid; all prescribed by their doctors, all nominally for therapeutic needs. The popularity of Enovid and the scarcity of reports of serious side effects encouraged Searle in 1959 to apply further to FDA for its registration as a contraceptive. The FDA required a new lower dose formulation for more women in another trial. Did Enovid actually work as claimed, as a contraceptive? Approval came in 1960 and sales of this already popular contraceptive boomed.

How combined oral contraceptives work in the body is complex, with multiple interrelationships. Their workings were poorly understood during the development time of 1950s to 1960s. The biological component of research leading to Enovid and other brands of pill was based on trial and error experimentation, starting with workers like Ludwig Haberlandt without even knowledge of anything called progesterone. Better understanding of how hormones worked, in terms of the molecular biology and genetics of receptor molecules and pathways was to come later. Currently it is known that progestin has various contraceptive effects. Cervical mucus becomes thicker, impeding travel of spermatozoa. Oviducts become less mobile, inhibiting movement of the ovum along the duct. Changes to the endometrium reduce the probability of the blastocyst implanting. Moreover, the progestin exerts a negative feedback on the pulse frequency of gonadotropin releasing hormone from the hypothalamus, which in turn causes a decrease in follicle stimulating and luteinizing hormones. The estrogenic component also reduces release of follicle stimulating hormone and so inhibits ovulation. Simply put: the Pill mimics the natural contraceptive effects of progesterone and estrogens during pregnancy.

In 1965 the Supreme Court of the United States made a ruling on the case of *Griswold v. Connecticut*. The ruling allowed contraception for any married woman in all of the nation's states. Estelle N.T. Griswold was a civil rights campaigner and Executive Director of Planned Parenthood in New Haven. Together with C. Lee Buxton, professor of obstetrics and gynecology at Yale University in 1961 she opened a birth control clinic in New Haven, breaking the Comstock Laws of Connecticut. The judges of the Supreme Court voted seven to two in favor of Griswold.

William Baird, known as Bill, turned from being a director of a firm supplying contraceptives in 1963 to a reproductive rights campaigner after witnessing in a hospital the ghastly consequences of a botched attempt at abortion by a woman who had poked a wire coat hanger into her womb. He took to distributing birth control literature in states with enforced Comstock Laws. He was imprisoned repeatedly. The appeal case of *Eisenstadt v. Baird* of 1972 resulted from a challenge set up with the help of students at Boston University. In 1967 they invited Baird to give a speech about abortion and birth control. Fifteen hundred people turned up to listen. To an unmarried woman student Baird handed over a condom and a packet of spermicidal foam. Promptly he was arrested on a charge that carried a maximum sentence of ten years in prison. He spent three months in a jail in Boston. That appeal case allowed contraception for unmarried women in all states of the nation. Ninety nine years had passed since the first federal law against birth control.

♦ ♦ ♦

Doctors, veterinarians and animal breeders understood long ago that a pregnancy prevents another pregnancy until birth is well over. Once the knowledge of hormones grew then one or more hormones were suspected as natural contraceptives. By the 1920s the therapeutic value of such hormones stimulated invention of methods to extract these natural hormones for animal organs. Concurrently the rapid growth of industrial organic chemistry provided methods for chemists to discover the structure of steroids. Then chemists learnt how to transform steroids and manipulate their properties. All the while the lure of good profits for improved hormonal drugs encouraged more firms to participate. Thus the invention of effective hormonal contraceptives was inevitable. Why then was that invention and its deployment so delayed? The contrariness of this story lies in the fabric of the peoples, societies and cultures such that contraception could first be considered obscene and immoral and then made illegal.

Humans are social animals: we cannot form a self-sustaining population unless we live and work and gossip and play together. Togetherness was our strength and adaptive advantage for finding food and defending against predators as we evolved. But living together is difficult: it requires discipline, negotiation and cooperative behavior. Necessary are conventions, taboos, norms, rules, laws, sanctions: morals in one word.

In species of mammal that live in highly socialized groups – chimpanzees, elephants, wolves, and others – instinctive patterns of social behavior predominate. We humans have evolved from ancestors who presumably had similar social instincts and all human cultures share a set of about two hundred behavioral characteristics that can

be called human nature. Of those behaviors influenced by hormones such as oxytocin, testosterone and estradiol, people in all cultures spontaneously and naturally show: emotions, affection, empathy, and sexual attraction. In addition we have mental abilities to understand much of the workings of our social world and to pass on that understanding through speech and writing. We deliberately devise new morals and revise older ones to give us advantage of a more deeply integrated sociality. But these deliberations are slow, uncertain, and prone to setbacks for human welfare that are only understood in retrospect.

From the original Comstock law of 1873 to the final rescinding of all such laws in the USA in 1972 there were huge changes in morals of the rights of women to vote and to take control of their own fertility. Campaigns for these rights emerged by the 1840s, focused first on the right of women to own and control their own property within marriage, and then on the right to vote. The Seneca Falls Convention, held 1848 in the state of New York, was the first conference on women's rights in America. At that time yearnings for better marital relationships in this patrilineal and patriarchal society were being publicly expressed. Campaigners such as Elizabeth Stanton, Victoria Woodhull and her sister Tennessee Claflinn developed powerful campaigning skills and publicity methods.

The most important property of the campaigners, their own bodies, was to be defended by a new moral right to refuse the sexual advances of their husbands and others. However, moral concepts of unwanted intercourse and rape within marriage were considered by most men as contradictions in terms. Men imposed a dominating social structure to allay their fears over inheritance rights and cuckoldry. One pillar of this structure was the ideology of motherhood; an ideology contrived by men and aided by women. Motherhood as a social virtue started with the role of breeding children as potential laborers within the family or as wage-earners in the wider world. It continued with the job of socializing the children, and the ideal mother was considered as gentle, undemanding and submissive.

A possible escape sought by the campaigners for women's reproductive rights was to change the ideology of motherhood. Some of them invented a concept of voluntary motherhood, discreetly incorporating elements of birth-control. But by the time countervailing forces, led by Anthony Comstock, got their law passed contraception became effectively illegal in many states. Voluntary motherhood as an ideal could not be seen overtly to promote the most practical method to realize the voluntary part: physical means for contraception.

Campaigners for and against birth-control battled on the public stage whilst in the privacy of the bedrooms of the nation something else was happening. During these times, in America and similar industrializing nations, women were conceiving less,

their fertility rate declined. In America of 1800 the fertility rate was 7.04 (average number of children typically born to a woman over her lifetime). Data for every decade up to 1940 declined steadily down to 2.10. Contraceptive methods were being used, although ignorance of contraception and reproduction remained common.

In 1905 US President Theodore Roosevelt made a speech to publicize his newly found enthusiasm for eugenics. He spread fear of what eugenicists called race suicide, their fear that if the better people of the nation did not breed fast enough they would become swamped by lesser people. Not only should the better people breed more but the lesser sort should be prevented from breeding. The objective was elitist discrimination more than controlling the size of the population. Eugenics was taken up with campaigning zeal by many well educated people from across the range of political opinion, left-wing to right-wing, outspoken socialists to vehement conservatives.

Many activists in the reproductive rights movement got swept along in this torrent of pseudo-science. They adapted the rationale of eugenics to boost their own simpler, straightforward demands for women to be treated with respect, as equals with men in the eyes of the law. They expected that their espousal of eugenics would give their concept of voluntary motherhood an aura of scientific respectability. What a deep trap of horrible irony they fell into! In America tens of thousands of women and men were deemed unfit to bear and raise children. They were forcibly sterilized. In parts of Europe the doctrine of eugenics led directly to the genocides and holocaust of the 1940s. Not until the news came out of these mass atrocities did eugenics retreat deep into the darker crevices and shadows of society.

Human social behavior is so complex because it operates far beyond the level of the instincts and simple learning of social animals with less powerful brains. Chimpanzees have rules of behavior but they do not have within their societies moral philosophers, life scientists, religious preachers, political campaigners, and courts of law equipped with legal libraries written over centuries. We construct our morality like a communal house. We work up from the biological foundations of our inherited human nature then we add whatever else by way of construction materials come to hand. Many people work over many lifetimes, with no single plan or knowledge of what will work other than what is gained by trial and error, or by the thought-experiments of philosophers and insights of preachers. A ramshackle cultural contraption is this house, contradictory and contrary. Our morality is the best we have for now, but as it developed from when we human primates gained our talents for thought and speech so it will continue to develop.

Sources and notes for Chapter 6

Hormones and reproduction

Anonymous, 2011. Family planning: a global handbook for providers. *World Health Organisation*.
https://www.fphandbook.org/sites/default/files/hb_english_2012.pdf

Allen, E. & Doisy, E.A., 1923. An ovarian hormone: A preliminary report on its localization, extraction, and partial purification, and action in test animals. *Journal of the American Medical Association*, **81**, 819-821.

Bridgham, J.T., Carroll, S.M., et al., 2006. Evolution of hormone-receptor complexity by molecular exploitation. *Science*, **312,** 97-101.

Eick, G.N. & Thornton J.W., 2010. Evolution of steroid receptors from an estrogen-sensitive ancestral receptor. *Molecular and Cellular Endocrinology*, **334**, 31-38.

Johnson, M.H., 2013. *Essential Reproduction*. Wiley-Blackwell, Oxford. [Integrates well the hormonal aspects of reproduction with its physiology and anatomy.]

Kushiro, T., Nambara, E., et al., 2003. Hormone evolution: the key to signalling. *Nature***, 422,** 122.

Laycock, J.F. & Meeran, K., 2013. *Integrated Endocrinology*, Wiley-Blackwell, Oxford. [A good example of the many textbooks covering clinical and biochemical aspects of endocrinology.]

Luck, M., 2014. *Hormones: a very short introduction*. Oxford University Press, Oxford. [A thought-provoking introduction to the subject.]

Sandor, T. & Mehdi A.Z., 1979. Steroids and evolution. In: *Hormones and Evolution*. Edited by E.J.W. Barrington. Academic Press, London. Volume **1,** 1-72.

Women's reproductive patterns

Allen, W.M., 1930. Physiology of the corpus luteum, V: the preparation and some chemical properties of progestin, a hormone of the corpus luteum which produces progestational proliferation. *American Journal of Physiology - Regulatory Integrative and Comparative Physiology*, **92**, 174-188.

Caruso, S., Agnello, C., et al., 2014. Do hormones influence women's sex? Sexual activity over the menstrual cycle. *Journal of Sexual Medicine*, **11**, 211- 221.

Corner, G.W. & Allen W.M., 1929. Physiology of the corpus luteum. *American Journal of Physiology*, **88**, 326-346.

Lobo, R.A., Mishell, D.R., et al., 1997. *Mishell's Textbook of Infertility, Contraception and Reproductive Endocrinology*. Blackwell, Malden.

Embryology and Pregnancy

Aplin, J.D., 1996. The cell biology of human implantation. *Placenta*, **17**, 269-275.

Carlson, B.M., 1999. *Human Embryology and Developmental Biology*. Mosby, St Louis.

Haig, D., 1993. Genetic conflicts in human pregnancy. *Quarterly Review of Biology*, **68**, 495-532. http://nrs.harvard.edu/urn-3:HUL.InstRepos:3153297

Held, L.I., 2009. *Quirks of Human Anatomy: an evo-devo look at the human body*. Cambridge University Press, New York. [See chapters 1 and 6 for accessible and inspiring accounts of examples of the contrariness of nature.]

Moore, K.L. & Persaud, T.V.N., 2008. *Before We Are Born: essentials of embryology and birth defects*, Saunders / Elsevier, Philadelphia. [Well illustrated account of human embryology and the anatomy of pregnancy.]

Invention and testing of progestins and hormonal contraceptives

Allen, W.M. & Ehrenstein, M., 1944. 10-nor-progesterone, a physiologically active lower homolog of progesterone. *Science*, **100**, 251-252.

Colton, F.B., 1955. 13-methyl-17-ethynyl - 17-hydroxy-1,2,3,4,6,7,8,9,11,12,13,14,16,17 - tetradecahydro-15H - cyclopenta [a] phenanthren -3- one and its preparation. *US Patent* 2,725,389. [The patent assigned to Searle & Co. for norethynodrel. http://patft.uspto.gov/netahtml/PTO/srchnum.htm]

Djerassi, C., Miramontes, C., L. & Rosenkranz, G. (1956). Δ4-19-nor-17α-ethinylandrosten-17β-ol-3-one and process. *US Patent* 2,744,122. [The patent assigned to Syntex for norethisterone. Djerassi commented in his paper of 1976 that the most cumbersome step of this invention of norethisterone was the reduction using lithium and ammonia; and many attempts were made to circumvent this industrial scale step. The patent describes it as follows. "*7.5 g of 3-methoxyestrone were dissolved in 750 cc of anhydrous dioxane in a three-neck flask, placed in a box and insulated with cotton wool. 2 l of anhydrous liquid ammonia and 15 g of lithium in the form of wire were added to the mechanically stirred solution. After stirring for one hour, 150 cc of absolute ethanol were added at such speed that no bumping occurred; when the blue color had disappeared, 500 cc of water were added in*

the same way. The ammonia was evaporated on the steam bath and the product collected with 2 l of water. It was extracted with ether and then with ethyl acetate and the combined extract was washed to neutral and evaporated to dryness under vacuum, leaving 7.4 g of a slightly yellow oil."
http://patft.uspto.gov/netahtml/PTO/srchnum.htm]

Djerassi, C., Miramontes, L., et al., 1954. Synthesis of 19-Nor-17α-ethynyltestosterone and 19-Nor-17α-methyltestosterone. *Journal of the American Chemical Society*, **76**, 4092-4094.

Ehrenstein, M., 1944. Investigations on steroids. VIII. Lower homologs of hormones of the pregnane series : 10-Nor-1 1-desoxycorticosterone acetate and 10-norprogesterone. *Journal of Organic Chemistry*, **9**, 435- 456.

Frye, C.A., 2006. An overview of oral contraceptives: mechanism of action and clinical use. *Neurology*, **66**, S29-S36.

Inhoffen, H. H. & Hohlweg, W., 1938. New female glandular derivatives active per os: 17α-ethynyl-estradiol and pregnen-in-on-3-ol-17. *Naturwissenschaften*, **26**, 96.

Junod, S.W. & Marks, L., 2002. Women's trials: the approval of the first oral contraceptive pill in the United States and Great Britain. *Journal of the History of Medicine*, **57**, 117-160.
http://ethique-tic.fr/2013/wp-content/uploads/1/2013/02/JunodMarks-pill02.pdf

Makepeace, A.W., Weinstein, C.L., et al., 1937. The effect of progestin and progesterone on ovulation in the rabbit. *American Journal of Physiology*, **119**, 512-516. [First demonstration of the hormonal effect of progesterone.]

Marker, R.E. & Krueger, J., (1940). Sterols. CXII. Sapogenins. XLI. The Preparation of trillin and its conversion to progesterone. *Journal of the American Chemical Society*, **62**, 3349-3350. [The start of Russell Marker's search for plant materials for progestin synthesis.]

Pincus, G., Chang, M.C., et al., 1956. Studies of the biological activity of certain 19-nor steroids in female animals. *Endocrinology*, **59**, 695-707.

History and politics of development of hormonal contraception

Allen, W.M., 2005. My life with progesterone. *American Journal of Obstetrics and Gynecology*, **193**, 1575-1577.

Anonymous, 2015. Percy Lavon Julian, Russell Earl Marker, and Carl Djerassi. *Chemical Heritage Foundation*

http://www.chemheritage.org/discover/online-resources/chemistry-in-history/themes/pharmaceuticals/restoring-and-regulating-the-bodys-biochemistry/julian--marker--djerassi.aspx

Chang, M.C., 1985. Recollections of 40 years at the Worcester Foundation for Experimental Biology. *Physiologist*, **28,** 400-401.

Colton, F.B., 1992. Steroids and "the Pill": early steroid research at Searle. *Steroids*, **57**, 624-630.

Djerassi, C., 1976. The manufacture of steroidal contraceptives: technical versus political aspects. *Proceedings of the Royal Society of London B*, **195**, 175-186. [See pages 177-178 for details of the original partial synthesis of norethisterone.]

Djerassi, C., 1992. *The Pill, Pygmy Chimps, and Degas' Horse*. Basic Books, New York. [The second of Djerassi's autobiographies. See chapters 4 and 5 for account of invention of norethisterone at Syntex.]

Djerassi, C., 1992. Steroid research at Syntex: the Pill and cortisone. *Steroids*, **57**, 631-641. [An alternative source of the above information on invention of norethisterone.]

Garcia, C.R., 1968. Gregory Goodwin Pincus 1903-1967. *International Journal of Fertility*, **13**, 267-9. [Biographical tribute to Pincus.]

Goldzieher, J.W., 1993. The history of steroidal contraceptive development: the estrogens. *Perspectives in Biology and Medicine*, **36**, 363-368.

Greep, R.O., 1995. Min Chueh Chang, 1908-1991, *National Academy of Sciences Biographical Memoirs*, pgs. 43-6.

Haberlandt, E., 2009. Ludwig Haberlandt – A pioneer in hormonal contraception. *Wiener Klinische Wochenschrift*, **121**, 746-749.

Ingle, D.J., 1971. Gregory Goodwin Pincus 1903-1967. *U.S. National Academy of Sciences Biographical Memoirs*. Pgs 227-270.

Jütte, R., 2008. *Contraception: a history*. Polity Press, Cambridge, UK. [A comprehensive, international, and densely detailed account by a historian.]

Lehmann, P.A., Bolivar, A., et al., 1973. Russell E. Marker. *Journal of Chemical Education*, **50**, 195-199. [A biographical tribute to Marker.]

Maisel, A.Q., 1965. *The Hormone Quest*. Random House, New York. [This is now dated in comparison with other accounts but has the advantage of being written by a journalist who closely followed this story as it happened.]

Marks, L.V., 2010. *Sexual Chemistry: a history of the contraceptive pill*. Yale University Press, New Haven. [A comprehensive account by a medical historian.]

Perone, N., 1993. The history of steroidal contraceptive development: the progestins. *Perspectives in Biology and Medicine*, **36**, 347-362.

Rosenkranz, G., 1992. From Rizika's terpenes in Zurich to Mexican steroids via Cuba. *Steroids*, **57,** 409-418. [Autobiographical account.]

Rosenkranz, G., 2005. The Early Days of Syntex. http://issuu.com/chemheritage/docs/syntex_rosenkranz-zaffaroni/0

Simmer, H.H., 1970. On the history of hormonal contraception. I. Ludwig Haberlandt (1885-1932) and his concept of hormonal sterilization. *Contraception*, **1**, 3-27.

Women's rights movement

Bailey, M.J., 2010. Momma's got the pill: how Anthony Comstock and Griswold v. Connecticut shaped US childbearing. *American Economic Review*, **100**, 98-129. [Mainly a mathematical analysis of the economic effects of contraception, with interesting conclusions.]

Baird, W., 2015. The real history of your right to birth control. http://prochoiceleague.org/history.html

Bullough, V.L., 1994. *Science in the Bedroom: a history of sex research*. Basic Books, New York.

Eig, J., 2014. *The Birth of the Pill: how four pioneers reinvented sex and launched a revolution*. W.W. Norton, New York. [The four are Sanger, McCormick, Pincus and Rock.]

Engelman, P.C., 2011. *A History of the Birth Control Movement in America*. Praeger, ABC-CLIO, Santa Barbara.

Gavron, S. 2015. *Suffragette*. Pathé et al. Film directed by Sarah Gavron, produced by Alison Owen, written by Abi Morgan. [A vivid portrayal of women's battles for rights using the example of suffrage in Britain around 1910; excellent leading acts by Carey Mulligan and Helena Bonham Carter.]

Gordon, L., 2002. *The Moral Property of Women: a history of birth control politics in America*. University of Illinois Press, Urbana. [A detailed analysis by a historian of how the moral politics about birth-control developed in America.]

Morality

Bekoff, M. & Pierce J., 2009. *Wild Justice: the moral lives of animals*. University of Chicago Press. Illinois.

Brown, D.E., 1991. *Human Universals*. McGraw-Hill Inc., New York.

Dennett, D.C., 2007. *Breaking the Spell: religion as a natural phenomenon*. Penguin, London. [Chapter 10 for material relevant to this story.]

De Waal, F., 1996. *Good Natured: The origins of right and wrong in humans and other animals*. Harvard University Press, Cambridge, USA. [A primatologist presents the evidence from his own and other's studies of biological origins of human morality.]

Goodson, J.L. & Bass A.H., 2001. Social behavior functions and related anatomical characteristics of vasotocin/vasopressin systems in vertebrates. *Brain Research Reviews*, **35**, 246-265.

Levy, N., 2004. *What Makes Us Moral: crossing the boundaries of biology*. One World Publications, Oxford. [An ethicist and philosopher examines the biological sources of human morality.]

Marcus, G., 2008. *Kluge: the haphazard evolution of the human mind*. Faber and Faber Ltd., London.

Pinker, S., 2002. *The Blank Slate*: *the modern denial of human nature*. Penguin, London. [A detailed examination of the biological roots of human nature. See the Appendix for 'Donald E. Brown's List of Human Universals'.]

Williams, G.S., 1996. *Plan and Purpose in Nature*. Weidenfeld & Nicholson, London. [Chapters 5 and 6 for material on sex and reproduction in humans.]