HORMONES—WHENCE AND WHITHER

Presidential Address*

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FELLOW Members of The Endocrine Society and Guests:

The entire group here this evening can be divided into two parts: 1) those who are interested in endocrinology, and 2) those who are more interested in endocrinologists. This being so, I shall offer, not heavy scientific data with which many of you are already overstuffed, but some thoughts along a lighter vein.

First of all, I should like to take you with me on a flight of fancy.

THE ORIGIN OF HORMONES

On this flight we shall talk first about life without hormones or, how hormones began. Let us think of life in the most general terms. As Krutch has said in his book, The Great Chain of Life, life can be divided into three parts: protein, love and death. We could begin with a protein, or we could even go back to a time preceding protein—by making an amino acid—but the evening is very short.

Love has been a popular subject for a long time. Let us begin with the premise that hormones began with love, and over millennia of time have, like love, become more complex. I must ask you, however, to think of love in a form primitive almost to the ultimate.

The forms of life we are acquainted with are concerned in so many ways with circulating chemicals, in animals and in plants, that one may well wonder what life really was like before hormones entered the scene. Did they come with sex or later? Did they perhaps precede sex with growth? But then, love is more interesting, so let us not be distracted.

Now for a few moments consider some of the low, or should I say small, forms of life. The single-celled paramecium, for example, contains circulating chemicals that must govern its growth, its digestion and perhaps its motion, but whether these can be called hormones is questionable. There is no reason to suppose that paramecia produce tropic hormones, although they do manage to find one another. Maybe this can be called "parameciotropism."

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1563
A paramecium has a remarkable way of reproducing. He just gets tired of himself and splits in two. This is called fission. Sometimes, however, 2 paramecia become particularly attracted to each other (Fig. 1). When they kiss (or conjugate)—and a very soulful kiss this must be—a part of the nucleus of each one passes into the other. Since this is a common-law wed-

![Figure 1](image_url)

ding, they part and may well say, to paraphrase the *Sonnets from the Portuguese*:

"Go from me yet I feel that I shall stand
Henceforth in thy shadow . . .
The widest sea
Doom takes to part us,
Leaves thy heart in mine . . ."

Incidentally, this is birth without death. Paramecia do not die, they do not even fade away, they just split in two. However, some do mate; but are hormones involved? It is marriage without children—a process that should be very interesting to Warren Nelson, and to Nehru also.

Now let us consider another tiny creature, the volvox. It is sort of half plant, half animal. It seems to have been the inventor of sex. It is obvious that Erasmus Darwin (who was Charles Darwin's grandfather), when he wrote *Temple of Nature* in 1804, thought that the various forms of life from the volvox up to the oyster were asexual:

"So safe in waves prolific Volvox dwells,
And five descendants crowd his lucid cells;
So the male Polypus parental swims
And branching infants bristle all his limbs;
So the lone taenia, as he grows, prolongs
His flattened form with young adherent throngs;"
Unknown to sex, the pregnant oyster swells,  
And coral insects build their radiate shells.”

So far as I can find out, however, volvox is the most primitive form of life that has ova and sperm, but whether or not it has hormones, I have not been able to find out. In a sense, I suppose it must have. Here, as elsewhere, there must be regulators both of growth and of reproduction. Apparently the volvox invented not only sex, but inevitable, natural death in the animal kingdom. Here we have a vague suggestion of hormones connected with love (Fig. 2), love with sex, sex with birth, and birth with death.

It has been stated that there were two great errors in the creation of the world. One is the inclination of the earth’s axis, and the other the differentiation of the sexes. If this be true, then volvox is a monstrous criminal. Biologically he is responsible for perpetrating the very origin of original sin. This is all vaguely reminiscent of the beginning of sex in religious mythology—a Garden of Eden if you wish. Under water where the volvox lives there are no trees, but you can see the apple-shaped ovum; the snake, however, is a little misplaced. Still, there is not much evidence of hormones, though I suspect that they are exerting their forces.

Let us leave volvox now and pay attention to another little fellow called hydra. Hydra is a small animal, the qualities of which depend, like our own, on protein, love and death. It lives in every pond, and it is smaller than a mosquito. It is actually a small tube with tentacles at one end. Each hydra is predestined to be either male or female. Both males and females at times are asexual, males growing buds that become males, and females growing buds that become females. If their pond water becomes stagnant, ova suddenly develop in females and sperm in males. This development is stimulated by a substance formed within them which, in
philosophical terms at least, is a hormone. Strangely enough, this hormone is none other than carbon dioxide, not in toto, not combined into carbonates, but the pressure of free CO$_2$. Thus, carbon dioxide becomes a hormone, and perhaps the first gonadotropin (1). This process is not so different from the regulation of release of hematopoietin by oxygen tension, nor from the stimulation of reproduction in birds by exposure to light.

All old stuff you say. Yes, that's true. We all like to appear erudite, though it is usually achieved by repeating the ideas and words of others. This system of trying to make oneself look smart is at least as old as Homer. As Rudyard Kipling says:

When 'Omer smote 'is bloomin' lyre
'Ed 'eard men sing by land and sea,
And what 'e thought he might require
'E went and took the same as me.

The market girls, the fishermen
The soldiers an' the sailors too.
They 'eard old songs turn up again
But kep' it quiet same as you.

They knew 'e stole
'E knew they knowed
They didn't shout an' make a fuss
They winked at 'Omer down the road
An' 'e winked back the same as us.

Bugs have hormones too; in fact, the lives of insects depend upon them. One is called the "juvenile hormone." It comes from glands (corpora allata) in the back of the insect's head. If these glands are removed when the insect is in the larval stage, the larva grows very little, yet will become mature. If extra glands from other insects are transplanted into the larva, or if it is given an excess of this hormone, it will grow too large but never become mature. This is the hormone of perpetual youth. (If it has not already been incorporated into facial creams, it surely will be soon.) What an interesting tool with which to study processes of growth without aging! In Figure 3 you see the possible result of the hormone of perpetual youth. The mother fly is greatly worried. The doctor with dignified abandon has diagnosed hyperjuvenilosis. This larva looks much like a eunuchoid giant. The human giant, like our bluebottle larva, grows excessively because of overproduction of a hormone from a gland in his head, and he also tends to remain immature.

**THE ORIGIN OF KNOWLEDGE OF HUMAN HORMONES**

We have considered life before hormones, and also some of the early evidence of hormones in biology. Now let us consider the long, slow dawning
on the human mind of the idea that there are hormones. This is not the "whence" of hormones, but it is the "whence" of our perception of them. By far the earliest knowledge of hormones came from observing man. The effects of castration and eunuchism apparently were understood in men long before they were in animals. Actually, the origin of eunuchism extends beyond any historic record and is lost in antiquity.

It is interesting that the earliest records of the idea of endocrine therapy are also connected with castration. You may be interested in some of the legends related to it.

The word "castrate" is derived from Castor (the beaver) according to a legend that appears in several ancient records, and was brought to us by a French translation called "Hortus Sanitatis" about 1500 A.D. The beaver was hunted for his glands from which "oil" was made (probably not as propionate, oenanthate, undecenoate, or even in a halogenated form) to cure symptoms supposed to be due to a lack of male hormone. The beaver, however, realizing that he was wanted only for this purpose, emasculated himself and thus escaped with his life. One of the old translations reads as follows:

"Castor when pursued by the hunter tears off his genitals, cuts them with his teeth, and throws them before the hunter. And when the hunter has obtained what he wants from the animal, no longer pursues him. And if any other hunter follows him he raises himself up and shows that he has no genitals, and thus avoids pursuit. And he is a very happy animal."

According to Greek mythology, castration goes back to the origin of the earth. In this myth, Cronus castrated his father Uranus; thus it was explained that heaven and earth were separated. One rather delicate
Touch to this story is that the operation was performed with a sickle made of diamond.

In some of the ancient religious cults the ministers were castrates. This was not, as we with puritanical background might think, with the idea of chastity, or to avoid the impurities or unholiness of sex. In those days, recreative power and reproduction were adored and not debased. Thus castration was performed in the spirit of sacrifice to ideals. For example, the ministers of the God d’Emésè in Syria were castrates. The cult was brought from Syria to Rome.

The origin of such ideas often was more intimately connected with fertility and re-creation of life than with anything suggesting hormones; yet the origins of our knowledge of both are inseparable. Rousseau says it nicely:

"The creative faculty, this insoluble problem of generation, this union of two to give the day to a new being which in his turn assumes the perpetuation of his race; there above all seems to have been the spiritual instinct of the first men. They adored the manifestation of the unknown, to their eyes the most certain sign of divine power. . . . Such emblems of virility signified to them the full force of divine creation."

Now I must tell you about the Legend of Attis and Cybele (Fig. 4). Cybele was a beautiful goddess, the Phrygian mother of the gods, the goddess of fertility. She conceived by a method which apparently was original with her—by placing a ripe pomegranate in her bosom. The god Attis was a young shepherd who, like many gods, was born of a virgin.
Cybele entrusted him with the care of her temple. Attis fell in love with a beautiful nymph; and Cybele, whom I suspect secretly loved Attis herself, put the wood nymph to death. Attis, in turn, in a fit of frustration and remorse at having been found unfaithful to his trust, castrated himself and died. In his place a pine tree grew, and from his blood upon the earth, violets sprang up.

The cult and the Attic rites were carried to Rome about 200 B.C. At their feast a pine tree was brought with dignity to the Sanctuary of Cybele. Its trunk was swathed like a corpse and its branches hung with violets. To quote Fraser’s “Golden Bough”:

"Stirred by the wild barbaric music of clashing cymbals, rumbling drums, droning horns and screaming flutes, the inferior clergy whirled about in the dance with waggling heads and streaming hair, until rapt in frenzy of excitement and insensible to pain they gashed their bodies . . . in order to bespatter the altar and the sacred tree with flowing blood. . . . Wrought up to the highest pitch of religious excitement they dashed the severed portions of themselves against the image of the cruel goddess. These broken instruments of their fertility were afterwards reverently wrapped up and buried in the earth or in subterranean chambers sacred to Cybele, where, like the offering of blood, they may have been deemed instrumental in recalling Attis to life and hastening the general resurrection of nature, which was then bursting into leaf and blossom in the vernal sunshine."

According to Matthew (chapter 19, verse 12), Christ said of eunuchs: "For there are some eunuchs, which were so born from their mother’s womb: and there are some eunuchs, which were made eunuchs of men: and there be eunuchs, which have made themselves eunuchs for the kingdom of heaven’s sake." Thus, from the recognition of the effects of castration, men learned in very ancient times to diagnose hypogonadism when it was spontaneous and not due to surgery.

The last religious cult to believe in castration was the Skopyt of Russia (Fig. 5). They were said to have number 17,000 as late as the year 1871.

It was a very long time from the beginning of such ideas in antiquity until the scientific method was applied and Berthold (2) first transplanted testicles and observed growth of the capon’s comb. The next great advance was not until 1927, when McGee (3) and Gallagher (4) in the laboratory of Dr. Fred C. Koch extracted testosterone from the testes of bulls.

THE FUTURE OF KNOWLEDGE OF HORMONES

Where are we going with hormones? or perhaps I should say, Where are they leading us? We have made a good start and have followed them a long way since the turn of the century and a much longer way in the past twenty-five years. The goal, however, is still not in sight; in fact, it is difficult to visualize a time when all knowledge of human hormones will be
complete, when all hormones are made synthetically, when their actions can be split into their component parts, when their production can be altered, accelerated, or diminished, and when abnormal balances can be abolished by such control. Perhaps it is through our very ignorance that it is possible to have such colossal optimism as to think we can master all the facts. In any event, we are still on the first leg of our journey; we must first learn "what is." Dr. Robert Seymour Bridges, a physician and Poet Laureate of England, in that most beautiful of poems, "Testament of Beauty," wrote:

"Wisdom will repudiate thee: if thou think or enquire WHY things are as they are or whence they came: thy task is first to learn WHAT IS, and in pursuant knowledge pure intellect will find pure pleasure and the only ground for a philosophy conformable to truth."

It would be trite to say that we are only beginning to learn what hormones there are. It would even be presumptuous to say to this learned audience that we must understand enzyme systems, receptors and mechanisms of action. It would be beside the point to tell you that new techniques are being supplied. What we must know eventually are methods for the detection of tendencies to hormonal disease before they begin. Eventually, this might involve selective breeding. But, here again our old friend Love, if not Death, may have a word to say.

Until these ideal states are reached we may advance by other steps. Glands will be transplanted and function normally, and perhaps mechanical or chemical glands will be developed. Already there are functioning
artificial lungs, artificial kidneys and, recently, artificial hearts. We are on the very threshold of an artificial pancreas, and I should like to show you one. The principles are demonstrated in Figure 6.

If we take the working parts of an auto analyzer and arrange continuous sampling of blood from a human being instead of samples from numerous test tubes, a continuous record of blood sugar concentration can be written automatically. If, instead of a written record, there is a trigger release for a microsyringe, insulin can be injected as needed. Already it is possible to
treat diabetic coma by such means (Fig. 7). The apparatus could be powered by a transistor. It could also be improved by adding other devices that would measure simultaneously the concentration of ketones, CO₂, or what you will.

This automatic method of injecting insulin is clumsy, but the first grandfather clocks were large and clumsy, and now watches can be made so small they can be mounted in a finger ring. Let us suppose that the mechanism shown in Figure 7 is reduced to the size of an ordinary bedside clock (Fig. 8). This could be encased in plastic and placed in the position of the spleen, which it might replace. When the splenic circulation is attached by Teflon tubes (such as those used for vascular grafts) to the splenic artery and vein, insulin could be supplied in amounts designated by the blood sugar levels. There would be no hypoglycemic reactions, as only the proper amount of insulin would be given; and no diets would be necessary. Refills could be obtained in small, sterile, disposable containers at any filling station.

Later, I suppose, chemical glands might be made. This invention is not yet complete, but the idea might be interesting to you. Let us make a chemical combination with insulin (Fig. 9). This complex is a substance, perhaps similar to glucokinase, or better still, sensitive to concentrations of both glucose and ketones. When the blood sugar concentration increases to more than 180 mg. per 100 ml., some of the glucose would combine with part of this complex, which would then liberate insulin in exactly the right amount, lowering the sugar content of the blood and stopping the release of insulin. Since 1 milligram of insulin supplies 22 units, which is close to a day's needs, an artificial implant of 1 gram of this compound might last about a year. The need for a refill might be determined by an enzyme-
glucose reaction in the saliva, as indicated by the color on the end of a toothpick.

But we must not allow our imaginations too much rein, so let us come out of orbit and back to earth.

When all the molecules of all the hormones are dissected and all the portions of all their atoms can be placed and replaced at will, what then? There will still be human beings with their proteins, their loves, their fears, their ambitions, their anxieties and their deaths. We are physicians, and let us never forget that we are working for the happiness of human beings. We must try to be patient, tolerant, and as kind as we would have our own physicians be to us. If I may be permitted another verse or two of poetry, let me recite the words of another physician-poet, William Henry Drummond, in “Ole’ Docteur Fiset,” a poem about a country doctor, in French Canada, who was the epitome of human kindness in medicine. The poem is rather long, so I shall recite only a few stanzas about the doctor and his old horse.

Ole Docteur Fiset of Saint Anicet,
   Sapre tonnerre! he was leev long tam!
   I’m sure he’s got ninety year or so,
   Beat all on de Parish ’cept Pierre Courteau,
   An day affer day he work all de sam

BASIS FOR A CHEMICAL 'BETA CELL'

Figure 9
Let her rain or snow, all he want to know
Is jus' if anywan's feelin' sick,
For Docteur Fiset's de ole fashion kin',
Doin' good was de only t'ing on hees min'
So he got no use for de politque.

An' he's smart horse sure, w'at he call "Faubourg,"
Ev'ry place on de Parish he know dem all.
An you ought to see de nice way he go
For fear he's upsettin' upon de snow,
W'en ole man's asleep on de cariole.

I 'member w'en poor Hormistas Couture
Get sick on hees place twenty mile away
An' hees boy Ovide he was come "Raquette"
W'at you call "Snowshoe," for Docteur Fiset,
An' Docteur he start wit' hees horse an sleigh.

All de night before, de beeg storm she roar,
An' mos' of de day it's de sam' also,
De drif' was pilin' up ten feet high
You can't see not'ing dis side de sky,
Not'ing but wan avalanche of snow.

Mus' be de Bon Dieu dat is help him troo,
Ole Docteur Fiset and hees horse "Faubourg,"
T'was somet'ing for splain-me, wall I don't care
But somehow or 'noder he's gettin' dere,
An' save de life Hormistas Couture.

Wall! Docteur Fiset of Saint Anicet
He is not dead yet! and I'm purty sure
If you're passin' dat place about ten year more
You will see him go roun' lak he go before
Wit' de ole cariole an' hees horse "Faubourg."

REFERENCES