# Current Biological Theories of the Sexes

The essence of what is discussed above proves: there were debates over the differences in the mental facilities of women and men. Other, heatedly fought over, debates covered the sexual differences in other physical or psychological features such as bodily strength. Some participants in those debates argued for sexual differences of the mind but also the strength of the body. Others argued against them. Debates moved between poles. It is an entirely different picture when considering the arguments stemming from procreation and features which became more and more actual markers of the sex with the progressing twentieth century: hormones, chromosomes, and eventually genes, too.

Whereas the theories of preformation easily presupposed the two sexes that were socially to be expected as different ones (also for the biological-medical theories of the sexes), the situation became a lot more complex under the eye of the developmental theories (the epigenesis): theorists could not only tie in when describing differences of two sexes, but also the sameness of them and the woman-and-man-being of every human individual at the same time.

## The Sexes between Brain, Muscles, and Microscopic Particles

The assumptions presented by Pizan and Gournay, Wollstonecraft and Bebel (the faculties and differences of the mind were the outcome of living conditions and those of society such as education and experience) seem

convincing. Natural scientists such as Darwin, Huxley, and Thompson shared them. Therefore, it seems the more surprising that scientific research into the brain (in the field of neurobiology) may still describe the differences of the brains of »women« and »men«, often regardless of their social background. Even if assuming the existence of pre-determined and unchangeable differences in the »female« and »male« brains (and their functions) one might expect that the counter-thesis (emphasizing the impact of socialization) may at least be recognized when devising such research – if for no other purpose than to hedge against the charge of being unsound in the methodology.

Anne Fausto-Sterling and Sigrid Schmitz have indicated exactly that problem for our current brain research, that of the late twentieth and early twenty-first centuries. It simply does not happen. When choosing subjects for research, it often does not even occur to the researchers that they are repeatedly drawn from the same pool of students from the own university. Their socialization and talents are rarely reflected. It might be of interest to look at, say, where and how a person was raised – whether in an urban or rural environment, poor or affluent – how the family was structured, whether they were showered with attention or neglected. Even more so (we are talking about brain research, so why not consider its most essential tasks?) what special skills did they acquire such as a foreign language, playing an instrument, communicating as a deaf person within a environment based on hearing, being exposed to a variety of stimuli in early childhood, physical exercise etc. What current challenges do occupy that person's mind? Is it a rather stressful or relaxed phase in their lives?

Those conditions for the research subjects are hardly addressed at all. People are found and committed as if just »fallen from the sky.« The subjects' brains are treated like biological machines created in uniformity just moments before research commences, not like brains belonging to people with a history. The hypotheses which are devised to explain the differences (of the sexes) that are identified on this bases project those brains back for many years – as if no one changes over the course of their lives. Then, in their projected times of embryonic formation or childhood, their development is solely considered the outcome of switched-on or – off genes and hormones as the core of found differences between human beings. Genes and hormones are the reason! Well, it is an assumption

which cannot be validated beyond doubt. The importance of socialization can be validated at least partially. Yet, it is utterly disregarded from the start. Whether or not such an approach is by design: it just allows researchers evidence of their own assumptions already entertained at the onset.

Just to emphasize once more (as this important aspect tends to be missed and keeping the argument of Beauvoir in mind): it is rather meaningless whether there are currently differences identifiable between »women« and »men.« It is important to consider those differences (which do exist) as part of the question whether they are the result of a »natural« disposition or the outcome of social inequality. As today's neurobiology (virtually) neglects the socialization of a person, the field is – please excuse the harsh choice of words – unfit to identify the reasons for those differences unless its methodology is adapted. Neurobiology may do little more than describe the product of the underlying reasons for those differences of today – sometimes in a more methodologically sound way than at others (see also Excursus 5).

Anne Fausto-Sterling and Sigrid Schmitz have indicated in their own current research that there are gaps in the methodology of neurobiology. They have discussed the methods of brain research critically and have shown just how the social presupposition of two different sexes was already at the starting point of most research endeavors (see Fausto-Sterling 1985, Fausto-Sterling 2000, Schmitz 2006; Jordan-Young 2011; but also Schmitz 2004 and Quaiser-Pohl 2004).

**Excursus 5: A Thorough Look into Biological and Medical Research and Their Methodology Is Worth the Time!**

Most often, employing the term »significance« for scientific research implies the thoroughness of the results. Here, however, it is interesting to consider the definition of the term. Statistical significance merely refers to an agreement. It »just« means that – with the stated probability – an observation likely is not the outcome *of utter chance*. Differences in statistical tests are referred to as significant if they were identified as having not occurred randomly with a probability margin of less than five percent. It means, that significance in itself does not suffice as a degree of plausibility.

Identifying the significance also entails considering the frequency of making spot tests as well as variations within the individual groups. Yet, it is equally helpful to consider for the actual research individual findings for the individual subject, but also to consider how those individuals were grouped in the first place. For example, some research have indeed found *significant* differences in the brains between the groups of »woman« and »men.« Looking closer into the results, however, also show clear variances within those groups. The following example may make things clearer:

Simon LeVay described significant differences of the INAH3 – a region of the anterior hypothalamus – for heterosexual and homosexual males as published in his *A Difference in Hypothalamic Structure between Heterosexual and Homosexual Men*. The region in homosexual males was apparently similar to those of women (who had not been subcategorized according to their sexual orientation). When referring to the following figure (7), however, it is striking just how great the variances within those groups are – for INAH3, too. They are hard to miss and cause more questions than give answers.

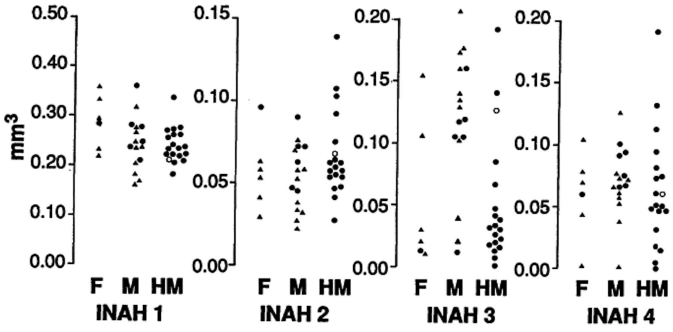


Figure 7: Differences in the sizes of the Interstitial Nuclei of the Anterior Hypothalamus (INAH) between women/females (F), heterosexual men/males (M), and homosexual men/males (HM); measures in $mm^3$ (as taken from LeVay 1991).

The region of INAH3 of individuals within the groups of heterosexual as well as homosexual males show results between 0.01 and 0.02 $mm^3$. In other words, results differ within one and the same group by a factor of 20. The measurements of those few women under research equally show such a great variance among the individuals of that group. One obvious conclusion should be that those regions may vary rather strongly from individual to individual in general – thus looking into explanations could be of interest. Socialization might be one factor but also the fact that many of the deceased homosexual males under research actually had contracted AIDS. While socialization did not play any role for this study, LeVay simply denied any influence AIDS may have on the outcome. Yet all measurements taken of INAH3 in the brains of »homosexual males« between 0.01 and 0.05 $mm^3$ were taken from the brains of individuals who had contracted AIDS (see LeVay 1991; Fausto-Sterling 1992).

LeVay's study subsequently enjoyed great popularity in the popular sciences, as did a study headed by Bennet and Sally Shaywitz (and their colleagues) in 1995. It appeared in the renowned journal *Nature*. The Shaywitz-study is still employed for making assumptions to an activation of the prefrontal lobe for *most language tests* (!) when attempting to conclude the different results based on sex. Yet, that study only looked into a limited number of regions in the brain, but more importantly, the Shaywitzes limited their findings to *recognize rhyme patterns* (!). While in male brains only the left lobe was activated for recognizing rhyme patterns, the Shaywitzes found that both frontal lobes were activated in females. The researchers had studied the brains of nineteen men and nineteen women. Eleven of those nineteen women actually did show an activation of both frontal lobes when being asked to recognize rhyme patterns. The other eight remained unmentioned in the article.

The study was also criticized for the fact that there was no description of the effect size – meaning, how much findings differed from individual to individual, that the number of subjects was very limited as was the number of regions in the brain under study. The

subjects' socialization was of no interest at all to the researchers. Such reference to the effect size is important, of course, as neurobiology presents us with colorful and bright representations of their findings in charts of the brain. Even the tiniest, and hardly measurable differences may be represented by the colors red, green, yellow, or blue – which appear significant but basically, like a smoke screen, signify nothing at all. Colors and their intensities on charts do not represent the degree of differences at all. For this, we need stated parameters of the study which come in numbers and are rarely colorful.

Despite their obvious methodological flaws, the studies of LeVay and the Shaywitzes (and colleagues) found their way into renowned biological journals (*Science* and *Nature*). Being renowned, however, does not make a journal infallible. A later study by Julie Frost and her colleagues did not find any difference between »women« and »men« at all when they attempted to re-create the Shaywitzes' study of recognizing rhyme patterns in 1999. Although their number of subjects was significantly higher (fifty for both sexes) and had considered more factors, that study did not reach the degree of popular attention the Shaywitzes did (see Shaywitz 1995; Frost 1999; Schmitz 2004).

The description of differences is also still a fact for other physical features. Here, too, it is rarely asked »whence and where to.« Often, scholars merely describe the state of today – which is then often simply taken as the result of biological factors. Inequality – whether based on dissimilar nutrition or exercises of the muscles – and its impact on physical and physiological features rarely plays any role at all when biologists consider the sexes. Everything we have discussed thus far, however, indicates that such inequalities clearly impact bodily features. Bourdieu and Fausto-Sterling today professed to this fact in their concepts of »habitus« and »embodiment«, respectively.

Yet, the works of Wollstonecraft, Marx, and Bebel indubitably profess to their early understanding of living conditions having not only an impact on the faculties of the mind, but also on the other physical features. They already outlined that it was possible to identify a person's »class«

by merely looking at them. Thus, it does not suffice at all to limit research into the differences of the sexes on simply describing just the way they are at the present: whether this or that bone is prolonged, this or that group of muscles has more or less fat embedded in it. It does not suffice any longer to then conclude those factual differences (of the sexes) are in themselves proof for their »naturalness.«

It is not merely the case that many of those studies themselves are already questionable in their methodology, or choice of subjects, as described above for those of the brain. Subjects are moreover already grouped as »women« and »men« from the onset. Those groups are then put opposite to each other, and differences suddenly appear meaningful. Yet, the variety of findings may be great even within one group, say »women« (see Excursus 5). Reasons for those differences are not sought but rather form the basis for the entire study: given differences are presupposed to be just that – given – and unchangeable. The reasons for them? Well, chromosomes, genes and hormones! What else?

It is worthwhile to turn to them for our discussion. One starting point are also the previously mentioned works by Fausto-Sterling.

A brief summary might be in order. The descriptions of differences of the sexes – and assumptions to their reasons – have been debated for quite some time now: whether regarding the faculty of the mind, peculiarity of the musculature and fat distribution, as well as other macroscopically visible features. Today, the scientist's last resort to preserve the safety and predetermination of such differences lie in microscopic aspects: chromosomes, genes, hormones. These are very complicated to challenge for a society, as criticism may easily meet the argument that, well, it takes a well-equipped (and thus expensive) laboratory to actually enter the conversation.

Other features of the certainty of an existing binary system of sex are also less discussed. The fact that there are two sexes, it seems, is rooted in procreation and thus serves the preservation of the human species. Two complementing sets of gonads and two blueprints of genitalia of the male and female sexes are merely the outcome of a »natural« necessity. Here, too, hormones, chromosomes, genes but also those chemical groups directly attached to them are particularly in the focus of scientists who explain that they cause a male or female development of the genitalia.

Thus, there is good reason to turn to this understood »core« of our knowledge of the binary sexes in the following – to those microscopic features. When wishing to question the currently prevalent biological theories about the human being as a sexually binary one (but also for raising the question of »female« and »male« equality or the existence of multiple sexes) a detailed discussion of the current scientific common ground is of the essence. This means addressing genetics, endocrinology, and evolutionary biology. Any reasonable suggestion for shaping society must be in accordance with the scientific »findings« of the times. Simone de Beauvoir, too, has stood firmly on the grounds of scientific research in her times.

The discussion below, however, will demonstrate that it is becoming harder and harder for current biological researchers to press their findings into a binary model of the sexes. Changing our perspective seems inevitable – away from two sexes toward many, from preformation toward epigenesis.

## Procreation as a Characteristic of the Species – and the Individual Form of Human Genitalia

Procreation is essential for the preservation of the human species. There is no doubt about that. The human agents of germination have been described as eggs/ovum and sperm since the nineteenth century. Both are cells that must conglomerate in order to form the basis for the embryo.

It may seem that all questions as to the sexes are answered by this statement, right? All previous discussions in this book have been rendered mute when mentioning eggs and sperm? Well, let us look into another argument: procreation is a matter of some people in our society, not all of them. Although we presuppose the people's ability to procreate when considering and classifying them – society has taught us to – yet it is often not even probable that they do. The state of Saxony, one of the East German Länder, for instance, has re-introduced subsidizing the artificial insemination which Germany as a whole had actually ended in 2004. They did so after a study found – or rather estimated – that fifteen percent of all heterosexual couples remaining without child without wishing to do so. The estimated number of unknown »cases« likely was higher, according

to the experts. Fifteen plus percent is a high number among the population, especially when considering that only some couples likely consulted a physician for their prolonged failure in procreation. Other couples may simply accept it, adopt, or become foster/surrogate – here meaning »honorary« parents to the children of relatives or acquaintances. Let us not forget that artificial insemination is not a guaranty for pregnancy – far from it. The risks are also considerable for the woman although this is rarely pointed out. In 2002, thirty-five to forty million inseminations led to about one million child births (see Berg 2003). Since Saxony had re-introduced subsidizing them in March of 2009, 552 inseminations helped start the lives of 112 children (see Tagespresse, and, among others, Block 2010).

When it comes to organic fertility, it is interesting to see the rather relaxed attitude of biologists and physicians dedicated to the development of the embryo. Studies on mice often demonstrate that »typically female« or »typically male« mice had developed. That those rodents are infertile equally often comes as an addendum. Infertility, the inability to procreate, apparently go well together with »typically female« and »typically male.« – Well, looking closer, we do the same when interacting with people in our everyday lives. There is more of a vague idea of fertility projected onto the specific people we deal with (rooted in our acquired understanding of what is »female« or »male«) rather than validated facts.

Popular as well as scientific considerations of procreation often simply forget, though, that the wish to procreate (or abstaining from it) is a personal one for every human individual. Political considerations of birth figures of a population which are apparently too low or their tastes, often see humans as potential »machines of procreation.« To have or to have not. Having children is a personal decision based on a personal background of one's own necessities and conditions of life. Economical and other social factors do play a role, no doubt, but the wish to have (or aversion to having) children is one of the most personal considerations of every human being. Every popular or scientific discussion of procreation should rest on that fact. Yet, they often separate the potentially presupposed ability to procreate from the ambition to actually do so. Asking about the personal and potential wish often remains forgotten.

These brief remarks already demonstrate that »procreation« is a problematic topic better to be seen with two perspectives. On the one hand,

procreation is a necessity to preserve the human species. Thus it is a »characteristic of the species.« Being part of the sexually reproducing side of the animal kingdom, human eggs and sperm need to meet in order to jointly develop into an embryo who is then born and nurtured. The wish to do so aside, it is statistically sufficient that – good health care and social caring provided – some ten or twenty percent of all humans procreate occasionally in order to keep up the numbers of a population (if that should be the driving force, however, is a topic for another discussion).

This »characteristic of the species«, on the other hand, does not say anything about the individual characteristics of the individual human being. A person does not have (or even wish) to personally have children. Just to be »organic« once more: there are multiple possibilities for genitalia to develop in an embryo, unlike a heart, liver, or lung – because they are not essential for the individual's survival. Malformations of the heart often lead to the death of the embryo or the infant if health care is insufficient to transform that heart into a state where it can function. Variations of the genitalia, however, do not lead to such negative outcomes for the individual as genitalia merely have to enable procreation which is crucial for the survival of the species but not for that of the individual. The formation of genitalia, too, is a developmental process into which a number of factors play. Thus, there likely is a greater variety of genitalia possible than for other organs – simply because there is no narrow corridor of the »correct« form for the organism in order to survive as it is compared to a heart.

Such considerations often meet the argument that one has to base all assumptions on »natural« requirements. We cannot – allegedly cannot, that is to say – consider health care or social caring, or the individual's wishes having an impact as »the primordial human being« did not command over such modern technological options of health care. Natural and humanity's history would be mixed according to this. The »natural« way of how other species procreate is another argument for comparison. Other animals are of no importance for our discussion for us. Their mode of reproducing – whether sexually or asexually – as well as the development of their sexes differ from species to species when compared to humans.

Human beings (and we discuss them in this scope) clearly profess to their »evolution« as being affected by economic and social conditions, health care, the individual's choices but also nutrition and caring for others.

Humans have changed the face of the earth everywhere according to their needs as no place remains untouched. Humans have devised atom bombs to eradicate themselves and other species if necessary. How on earth, to ask bluntly, should a distinction between »natural« and human history work? It would require a certain lack of understanding of the last ten thousand years of human social, historical and scientific development. Human history is part of our natural history – as the history of other species is part of natural history, too. Natural history, seen differently, is equally part of ours. Evolution – spurred by nature but later also by humans – led to more and more complex organisms and, eventually, to the modern human one.

## The Formation of the Genitalia in the Development of the Embryo

Let us turn to the stages of the genitalia's development of a human embryo just as it is described in developmental biology before turning to chromosomes, genes and other factors such as hormones (see Excursus 6) (see Voß 2010: 242 et seq.; Ainsworth 2015).

Today, our comprehension largely follows the historical understanding described above: one embryo is not sexually distinctive from another in an early stage of their development. Genitalia are described as »neutral« or »bipotential.« According to this, every human embryo has the potential in their first weeks of development to grow into a more or less »female« or »male« one. The term »bipotency« alone, however, indicates only two possible outcomes are at the core of considerations. Actually, the idea is for the embryo to develop its gonads in the first phases of the genitalia's formation. There are allegedly only two possible varieties – testicles versus ovaries – whose subsequent hormonal release would engineer any further sexual development.

We currently understand the appearance of gonads in an embryo to take place around the fourth week of its existence. They remain in their bipotential stage described above until the seventh week. Then, the embryos show more and more differences, professing to their »female« or »male« direction of development. Two tissues seem crucial for the formation of the gonads: one of them is the coelomic epithelium (also called

somatic mesenchymal cells) which become the somatic (physical) tissue of the gonads. The other crucial tissue are primordial germ cells (also known as gonocytes) which infuse into the somatic tissue and form gonads there. The primordial germ cells' infusion takes place in the sixth week of the embryo's development. It may be the result of the coelomic epithelium sending out chemical »attractants.« That phase of sexual bipotency also witnesses the formation of the Wolffian/mesonephric duct and the Müllerian/paramesonephric ducts. Both later play a role in the differentiation into »female« and »male« genitalia.

*Development of the testicles:* The somatic cells further differentiate into »Sertoli cells.« Around the eighth week of the embryo's development, they organize the testicular cords. The testicular cords comprise germ cells which form into »spermatogonia« and, following division and differentiation, into spermatozoa from puberty onward. All germ cells outside of the testicular cords wither. The »Sertoli cells« are crucial in the embryo's further development as they release the »Anti-Müllerian Hormone« (AMH) which causes the Müllerian duct to regress.

Somatic cells which have not taken part in in the formation of the testicular cords develop into »Leydig cells«, situated between the testicular cords. They produce testosterone from the eighth week of the embryonic development onwards – up until the eighteenth week they are particularly induced to do so by the mother's human chorionic gonadotropin (hCG). Later than that, the pituitary regulates the production of testosterone through the luteinizing hormone (LH), also called interstitial cell-stimulating hormone (ICSH). Testosterone in turn affects the differentiation of the Wolffian duct to epididymides, ductus deferens, seminal vesicle and the exterior sexual characteristics. Both testosterone and the equally influential dyhdrotestosterone (which belong to the group of the »androgens«, the so-called masculinizing hormones) take their affect from attaching to the »androgen receptor.«

*Development of the ovaries:* Here, the Somatic cells differentiate into a cortex area (a connective tissue dense in cells) and the »marrow«, which is less dense. The germ cells remain in the cortex area for the development of the ovaries. The embryo's gonadal cords – which in a male development evolve into testicular cords – regress. There is a development of secondary gonadal cords in the cortex area instead. Germ cells, which are comprised

in the cortex area, form primordial follicles by multiplying and covering with a single layer of follicular epithelial cells which have formed from the secondary gonadal cords. The germ cells enter into the prophase of the first maturation division of meiosis. They remain in that phase at least until puberty. Then, the primordial follicles mature »primary«, »secondary«, and eventually »tertiary follicles« after being induced to do so by the »follicle stimulating hormone« (FSH).

This period until puberty equally witnesses a halt of the further gestation of the follicular epithelial cells. They then become »granulosa cells«, which release – aromatase, an enzyme (again, induced by FSH). Aromatase plays a role for the conversion of testosterone into oestradiol, a member of the family of estrogens. They are the hormones which are considered to be important for »female sexual development.«

The granulosa cells are for the formation of the ovaries what the Sertoli cells are for the offspring sporting testicles. Theca cells, on the other hand, correspond to Leidig cells. Theca cells do in fact form the layer of cells that surrounds the follicles. Just like Leidig cells, theca cells equally react to the luteinizing hormone the pituitary sends their way, and androgens (testosterone and androstendione) are produced as a result of that. Under the influence of the enzyme aromatase said androgens are converted into estrogens (see Excursus 6).

Just why the Wolffian duct regresses in the development of ovaries while the Müllerian duct moves forward, remains unclear. Until well into the 1990s, studying the development of embryos meant studying that of »male« ones. Just how female ones come into being was deducted from that! One explanation for what we see, the regress of the Wolffian duct was explained by the absence of testosterone, while the further development of the Müllerian duct was considered the outcome of absent AMH. In other words, certain conditions would lead to the development of testicles. If those conditions were absent, ovaries result in an utterly passive way. That there might be some active steps in the development of ovaries involved is a more serious consideration of studies from the 1990s onward. Whatever those studies may find: we do know that the Müllerian duct further differentiates into fallopian tubes, uterus, cervix, and upper vagina.

It should be clear by now that the common dispositions for the development of the sexes are overwhelming. Germ cells as well as the Wolffian

and Müllerian ducts are common to all embryos in the initial stages; granulosa and Sertoli cells, theca and Leidig cells also correspond to one another and develop out of the same embryonic origin. Androgens equally form in all embryos. They are simply converted into estrogens in different quantities (see Excursus 6). Thus, is it not imaginable – the following will make it clearer that it is more than an imagination – that the sum of factors, moments and quantities of their availability, differ from individual to individual? It is equally clear (in fact a truism) just how co-dependent the development of the embryo is to factors coming from the mother's body.

All considerations also lead to conclusion that a simple »either – or« (either testicles or ovaries) cannot be a fact for the development of the germ cells – least of all for the formation of the other parts of genitalia from there. No, all (biological) considerations have to lead to one notion at least: there might be a variance in the formation. It may be the result of factors having an impact on some areas of the forming tissue only. Cells may form receptors for androgens or estrogens in variance to the concrete blue prints studies have allegedly identified.

There is a more variegated picture when it comes to the possibilities of how genitalia are formed. It is worth finding a new classification of our findings – one which does not presuppose a binary »nature« of the sexes. It should be worth our while to break with a mode of thinking which disqualifies variances as »disturbances« or »digressions« of a »normative development.« A new classification should moreover lead to a better and (for this time being) more convincing description of the variety of the manifestation of the sexes which actually presents itself.

### Excursus 6: Biosynthesis and the Effects of Androgens and Estrogens

Most often, androgens and estrogens are presented as opposites. The first have allegedly a masculinizing effect; the latter a feminizing one. It is equally assumed testicles produced androgens, ovaries estrogens. This, a closer look may be advisable.

Androgens and estrogens are based on biosynthesis which is more or less the same for both. As steroid hormones they go back to cholesterol. Androgens are the descendants of pregnenolon (or progesterone, which is a product of conversion). At an initial step,

they form the androgens *androstenedione* and *androstendiol* that eventually become *testosterone*. Those androgens – particularly in connection to the enzyme aromatase – converted into estrogen. Thus, androstenedione becomes the estrogen *estrone*; testosterone *estradiol.* Androgens are therefore always the basis for the conversion of »estrogens.«

The biosynthesis of androgens and estrogens do most often – but not exclusively – take place in the germ cells. Countering examples are the formation of androgens in the adrenal cortex, or of estrogen in the placenta. Such production also takes place in other tissues but only in very moderate quantities. If androgens reach a high concentration, they may be converted into estrogens in the fat tissue.

It is common wisdom that androgens and estrogens affect the formation of primary and secondary characteristics of the sexes. That wisdom actually neglects their other effects, though. Estrogens seem beneficial for the wellbeing of the heart, the growth of bones, and the formation of sperm cells. Testosterone, on the other hand, seems to affect the blood circulation system, blood cells, liver, but also for burning fat and carbohydrates. There is no doubt, estrogens and androgens are both very important for »women« and »men.« Anne Fausto-Sterling rather suggests classifying them as »growth hormones.« »Sex hormone« simply conceals the entire scope of their effects.

The hormones' quantity and interdependency seem important. The various cells of the forming gonads interact and react to stimuli (given they possess the corresponding receptors). Enzymes/emzyme complexes or other complexes of proteins are necessary to from androgens and estrogens. They, in turn, only have an effect when the corresponding receptors to connect are present in the cells. Only then can androgens and estrogens initiate reactions. Thus, their effects may differ according to the individual conditions and influences.

The other conclusion this leads us to is, of course, that a mere »high concentration« of androgens does not necessarily means a masculine appearance. A body lacking the receptors for andro-

gens or providing large quantities of aromatase which convert said androgens, may appear utterly »female« despite a »high concentration« of androgens. Then, the problem is not the forming appearance, but society's typical disease mongering the varying concentrations of hormones. Five to fifteen percent of all women at the »child-bearing age«, for instance, are described as sick just because they form too much »masculine« hormones (see, among others: Ebeling 2006b; Stryer 1999 [1995]: 739 et seq.; Horn 2009: 398 et seq.; Schartl 2009: 719 et seq.).

It is not exactly news that estrogens and androgens are present (and have an impact) in men and women alike. Is has been described since the 1920s (see Oudshoorn 1994; Fausto-Sterling 2000; Sengoopta 2006).

## Gonads, Germ Cells and Eventually Chromosomes and Genes: Do They Prove Sexual Binarity?

»Testicles« in particular have been in the focus of research since the 1700s. They have been assigned special »sexualizing« features. In the beginning, only »male testicles« were described as masculinizing the organism. Then, at the begin of the nineteenth century, »female testicles« (ovaries) were considered and described. In the common understanding, they were seen as the main organs for feminizing an organism. The chronological order (first researching the »masculinizing effects«, only later the »feminizing« one) is a leitmotif for the biological-medical sciences. The starting point then was – as described – to see the man as the perfect formation of a human being who was superior to the imperfect version seen in the woman. Based on this, the formation of a man allegedly required certain additional developmental steps that were missing in the development of a woman. It was an androcentric stance not uncommon to the biological-medical studies.

Through this focus on the »male testicles« and »ovaries« they were assigned far-reaching functions. Rudolf Virchow (1821–1902) was an important (and otherwise progressive) physician and social policy expert whose involvement brought important hygienic institutions to Berlin in

particular such as the first communal hospitals, canalization, and central drinking water supply. On the gonads, he wrote:

> »Woman is a woman just because of her gonads. Ignore all peculiarities of her body and mind or her nutrition and nerve activity: all sweet gentleness and rounding of the limbs with the peculiar form of the hips, the development of the breasts while the vocal organs remain unchanged, that beautiful decoration of the hair on her head and the soft, hardly noticeable down of the remaining skin, and then the depth of her emotions, this truth of immediate recognition, this sweet temper, dedication and faithfulness – in short, everything we admire and revere in a true woman: it rests on her ovaries alone. Take away the ovaries and you will face that mannish woman in all her ugly in-between-ness: coarse and rough shape, strong bones, the moustache, the rough voice, flat chest, the envious and selfish soul and the crooked view of the world« (Virchow 1856 [1847]: 747; footnotes omitted).

It is clear what importance was given to ovaries (and testicles). Ovaries and testicles were seen as the sexualizing features. Not only did they held sway over how a human body was formed physically but also its personality and moral dispositions. Virchow's quote demonstrates the vivid – and often overwritten – language that was commonly used to describe the differences of the sexes then.[28]

In the beginning twentieth century, the belief in the gonads was so strong that scientists considered the benefits of transplanting the tissues of testicles and ovaries, later of the substances isolated from them (the »hormones«). In their eyes, it would have an impact on the formation of physical, physiological, and psychological features. Of course, those tissues and their substances were believed to have a rejuvenating effect as well.

A parallel understanding developed at the same time – we are still at the turn of the twentieth century. Rather than considering the gonads, researchers focused on the substances of procreation: egg and sperm cells. As we saw in our historical overview in the last chapter, natural philosophi-

**28** As a side note and recommendation: Londa Schiebinger described that scientific language so excellently for the field of botany in her *Das private Leben der Pflanzen [The Private Lives of Plants]* (Schiebinger 1995).

cal and biological-medical considerations of the sexes revolved around the importance of these cells. The theories of preformation, on the one hand, understood the substances of procreation to be fully formed grown »men« or »women« – albeit in a tiny version. The theories of development, on the other hand, saw the substances of procreation being an »unformed matter« which would develop and differentiate. There were also several approaches to explain the difficult issue of the children resemblance to both their parents.

With the progress of the microscopes (and thus the microscopic research, of course) the cellular structure of »eggs« and »sperm« was eventually understood in the nineteenth century. Karl Ernst von Baer (1792–1876), a German researcher in Estonia, scientifically described the »egg« in 1827. In 1841, Rudolf Albert von Kölliker proved that sperm was tissue and not tiny, fully animated living beings (although we still use the term »spermatozoon«, which means just that: seed living being). Oscar Hertwig (1849–1922) eventually described how the egg of a sea urchin was inseminated (those eggs are popular among researchers for their size).

The morphology of »chromosomes« has been known since the 1840s. They were described in detail and for their possible function in matters of heredity in the 1880s. It was the German Theodor Boveri (1862–1915) who in 1904 described the mechanisms of the chromosomes' reduction and distribution in the formation of the germ cells (meiosis). He also demonstrated that homologous chromosomes paired when egg and sperm cells fuse.

The 1890s brought the understanding that the chromosomes played a role in transmitting the sex to the offspring. Hermann Henking (1858–1942) demonstrated that – as a result of meiosis – two versions of sperm cells appear: some contain a certain, large element of chromatin, others do not. Following up on this, researchers such as the Americans Nettie Maria Stevens (1861–1912) and Edmund Beecher Wilson (1856–1939) made similar observations in several species of insects. Some species presented an additional element of chromatin in a part of the sperm cells (which was absent in others). Some species showed one pair of chromosomes whose partners clearly differed from one another. In 1909 and 1911, the smaller of these chromosomes was termed »Y-chromosome«, the larger »X-chromosome.« Theophilus Painter

(1889–1969) outlined in 1923 for human beings that the cells of male individuals possessed a pair of X- and Y-chromosomes, females had a pair of two X-chromosomes. Painter concluded that the decision over the sex of human being rested in the chromosomes (see Voß 2010: 209 et seq., 246).

Today, this understanding of a clear differentiation of the chromosomes according to sex often leads to a hasty conclusion: well, the debate is over. There are – only! – two sexes! Such a conclusion is as incorrect now as it was for the 1920s. Then, as it might be recalled, the theory of intermediate stages considered the factual existence of sexual variances. Moreover, the conclusions according to chromosomes did not necessarily stand in opposition to that theory.

Richard Goldschmidt (1878–1958), a renowned zoologist of his time, presented his understanding of the chromosomal sex as being female or male. Yet, he also concluded that all individuals harbored the disposition to both sexual characteristics – female and male – which he called »factors« of femininity and masculinity. Goldschmidt studied insects – like most of his colleagues did, in particular (gypsy) moths (Lymantria dispar) – but transferred his findings to all animals, humans included. Depending on the species, the factor of femininity or that of masculinity would be localized on the X-chromosome – and thus may be present »twice« – whereas the other was on the Y-chromosome. For some species, Goldschmidt assumed them on the autosomes (the remaining chromosomes of the »body«).

Quantity, timed influence and speed of the reactions of both factors would differ – especially because of the different position in the chromosomes. The predominant factor determined the sex. Although one factor often permanently dominated the other, another interaction was possible. Sometimes, Goldschmidt believed, factors would take turns in their dominance in one and the same individual. He referred to the point in time as pivot, i. e., when one factor took over the dominance from the other. Depending on how early or late that pivot occurred, the eventually dominant factor had a greater or lesser impact on the physique, physiology, and psychology of the individual. Goldschmidt outlined an »unbroken line of succession of transitions« in the formation of sexual characteristics; »femininity« and »masculinity« were »extreme poles« of this line. It is very difficult to ignore the similarities between Goldschmidt's under-

standing and that of the theory of intermediate stage (see Voß 2010: 212 et seq.).

Goldschmidt's assumptions were popular among scientists as well as laypeople (see Satzinger 2009: 259 et seq.). Paul Kammerer (1880–1926) was an Austrian biologist who thoroughly studied heredity concluded from them that »There are only hermaphrodites.« One of the chapters of his book which appeared in 1927 was titled as such. Then, Kammerer wrote that

> »the germ cell – as it was said – is home to both male and female dispositions. One is preferred over the other and therefore dominates the development in an undisturbed manner. Yet, the other is never utterly suppressed as it is always present in the form of stunted organs of the other sex [...] Whether the latent or potential bisexuality of the germ transforms into the current, visible bisexuality of the hermaphrodite depends on both dispositions of the sex being in an equilibrium (or close to it). When they are not, one is more dominant than the other. This disposition thus determines the ›purity‹ of the adult's sex. The more the development of a ›split-up sexual organism‹ (*getrenntgeschlechtliches Lebewesen*, in the original German) is progressed, the more the preferred sexual disposition prevails. Because the process is far from being a sudden one, there are no clear boundaries between the hidden hermaphroditism of the germ on the one hand and the seemingly single-sided and allegedly pure sexual nature of the adult on the other hand. There is no complete conquest of the other disposition as there will always remain some form of remnant. In other words: there are no strictly ›split-up sexual organisms‹. There is, to be exact, but one single sex – or better, one sex of a dual nature: the hermaphrodite. *Every individual is hermaphroditic to some degree:* even the most virile of men harbors female elements; the most feminine woman has male elements« (Kammerer 1927: 81 et seq.).

It is a curious (and for the following quite important) fact that Goldschmidt never understood the chromosomes to dictate the development of the sex. It was rather a composite of chromosomes and other influence from within the cell and the organism. Goldschmidt's contemporary Thomas Hunt Morgan (1866–1945) theorized in America a different

model of interaction according to which one specific gene produces one specific enzyme. For his theory, Morgan rested on the researches in cross-breeding strands of fruit flies (drosophila melanogaster). He argued that a definable segment on a chromosome (a gene) leads to a protein (enzymes are proteins) or the respective feature of an organism.

The theory is still considered valid for fruit flies and their so-called »mono-genetic diseases« (meaning »de-formations« of the flies' features that can be traced back to one gene).

The difference between Goldschmidt's and Morgan's hypotheses is as such: Goldschmidt saw the effect of the chromosomes in connection to processes of the cells and the organism in general. Genes were active on different levels of a hierarchy. Morgan's concept was a little more simplistic: chromosomes and genes had the sole say in the development of characteristics and features. The cells were merely the location where it happened (or tool, if you will).

Harmonizing both concepts would have been worthwhile for the further evolution of science. The teachings of Goldschmidt, however, ended with the German Fascists persecuting and killing its main representatives. When the National Socialists gained power, Goldschmidt's conditions for research took a turn to the worst in Germany. In the ductus of the racial ideology then he was considered Jewish. After his emigration to the US in 1936, Goldschmidt lost the favorable research environment he had in the Berlin Kaiser Wilhelm Institute of the 1920s.

The study of hormones also lost that understanding of a more complex interaction. Bernhard Zondek (1891–1966) was influential in the research of hormones, too, then. As he was also Jewish, he emigrated as well – to Palestine in his case. He had found, for instance, large quantities of »estrogen« (»feminizing sexual hormones«) in a stallion. Adolf Butenandt (1903–1995), on the other hand, was one to remain in Germany – as a member of the Nazi-Party and who was later a Nobel laureate and president of the Max Planck Society.[29] Thus, he set his own mark on the understanding of hormones. His rather simplistic model presented hormones as the

**29** The Max Planck Society for the Advancement of Science was formed in 1948 as successor to the Kaiser Wilhelm Society. It is a formally independent but state funded association of Germany's foremost research institutes. The translator.

sole agents of forming the sexes – despite the fact he found discrepancies in his scientific research. The model he propagated, however, neatly tied in with his own understanding of clear boundaries between the sexes in matters of biology and social as well as family duties (see Satzinger 2009).

The German Fascist ideology ripped a gap into our understanding which initially could not be closed even after World War II ended. Goldschmidt's theories remained overlooked well into the 1980s (see Satzinger 2004: 6 et seq.). When James D. Watson and Francis Crick (in collaboration with Maurice Witkins) published their molecular structure of DNA in 1953, the »belief« in the importance of DNA and »genes« prevailed. As a side note: Watson and Crick used the x-ray structural analysis of Rosalind Franklin (1920–58), a member of Wilkins' team. They never even mentioned her name when they accepted the Noble Prize four years after her death.

Subsequently, biological and medical research was predominantly funded if seeking to understand genes – systemic research rather remained in its shadow as underfunded and with a rather marginal public perception. The same fate befell theories of a more complex understanding of genes as the creed of a »static genome« still prevailed. Barbara McClintock (1902–92), for instance, was initially ridiculed for her contradictory results. Her path breaking studies of »transposable elements« from the 1940s were finally recognized as late as 1983 when she received the Noble Prize. Only then did they achieve a more dominant role in research considerations. Systemic research that include the cells and the entire organism as well have covered ground again from the 1980s onward. Yet, it also took the rather disappointing results of the human genome project of 2001 which proved that decoding genes does not mean anything if ignoring a more complex interaction.

Thomas Kuhn (1922–96), the American historian of the sciences, quite rightly asserted that »no part of the aim of normal science is to call forth new sorts of phenomena; indeed, those that will not fit the box are often not seen at all. Nor do scientists normally aim to invent new theories, and they are often intolerant of those invented by others« (Kuhn 2012 [1962]: 24).

It is crucial to consider the influence politics and funding have on current studies in biology and medicine. Yet, it is equally vital to understand

just how the idea of fitting results into the dominant boxes in the fields turn study results into theories. Those which do not (or did not) fit actually have existed but have rarely formed the dominant theories.

Let us not forget the »big« social frameworks which foster the dissemination of some theories over others. Those who benefit from a social order will, as mentioned, also prefer theories of stagnation and predetermination: they were not in such a cozy position because of social inequality but rather because of the »given skills they were born with.« True, education may bring inherited skills to full fruition but other people could not live up to that potential. Those who do were just incapable to excel themselves through such an education because of their »natural« disadvantages. Even today such a point of view is a rather widespread ideology.

Another of those frameworks of society does not reveal itself so easily. At first glance, we may identify an opposition between genetics and the Christian church. However, there hardly is one. Their teachings may go hand in hand – if only on the basis of *predetermination of the inevitable*. Genetics describes molecules which already harbor the complete set of information – they merely need to be heard. The Christian church, of course, takes recourse with »God« as the predetermined and final authority. »God the Creator« also easily explains for genetics just how that information has gotten into the genetic material. When we contrasted the theories of preformation and those of development for the seventeenth and eighteenth centuries, it was clear that the natural philosophical idea of preformation could rest on a Christian-clerical worldview. It may have been amusing to read about the belief of sperm or egg containing a tiny person. The current prevalent understanding of genetics is not so different, though. There, too, genes harbor the information for the individual parts of the body – a tiny person waiting in our genome, so to say.

Nothing is generated out of the vacuum. There is a certain socio-historical background against which Evelyn Fox Keller could refer to the twentieth century as *The Century of the Gene* (Keller 2000). Further study results have to be understood in the same light.

Thus far we do know that testicles have played an important role. They even gained importance with the studies of the French Alfred Jost (1916–91) from 1947. For his experiments, he removed the undifferentiated gonads of rabbit embryos in the early stages of their development.

Subsequently, no matter what the chromosomic combination of the rabbit embryo (whether »female« or »male«), the embryo always developed »female« characteristics toward fallopian tubes, uterus, vagina and female external genitalia. Jost concluded that a »female« development did not need gonads (ovaries) but the male one does (testicles). That experiment, and Jost's conclusions, formed the basis for later research. It became the dominant reading of the genetic paradigm which itself set the standard (see, among others, Rieder 2003).

1959 brought forth two other path breaking works: patients who harbored only one X-chromosome (but not the other or a Y-chromosome) had a female appearance (ovaries included). Their »X0-set of chromosomes« is commonly referred to – and pathologized – as Turner syndrome. Those patients with two X- and one Y-chromosome – »the XXY-set of chromosomes« and equally pathologized as a variation of the Klinefelter syndrome – developed male features. This did allegedly prove the peculiar importance of the Y-chromosome which – if present – inevitably leads to the formation of testicles.

Since then, the 1950s, scientists have searched for the chromosomic and genetic factor that enables the formation of testicles. Again, we may see the androcentric leitmotif in this: scientists always started at the assumption it was only the male sex that developed. That kind of research also started the quest for the particular segment of the chromosome (and at the beginning it was one singular sought-for segment) which would determine the testicles. Such testis-determining factor (for humans abbreviated to TDF, for the main organism of research as Mouse Tdy) was believed to induce the development of testicle in one single step. All further development toward »male« characteristics would depart from that.

Following the findings of 1959, TDF's location was assumed to be on the Y-chromosome. Therefore, it was under intense scrutiny. In 1966, scientists narrowed the area to short arm of the Y. Since 1975, several scientists identified several areas (»genes«) on the Y-chromosome as the culprit. Assumptions to have found the home(s) of TDF always ended in a dead end. There were just too many exceptions: either the area was present in several individuals who stubbornly still did not develop testicles, or individuals had them but not a trace of the supposed TDF-area on their Y-chromosome. Equally frustrating must have been to identify the area but

then finding numerous copies of it on numerous chromosomes of their genome. That it was responsible for developing testicles only then became less and less probable.

In 1987, David C. Page and his colleagues suggested a gene which they also found on the short arm of the Y-chromosome: ZFY. Its product, the ZFY protein, demonstrated clear chemical structures of a transcription factor, i. e., one which »switched on« the expression (meaning reading) of other genes. Thus, ZFY was initially believed to be the testis-determining factor. Yet, again, research into the development of the sexes of marsupials and rodents told a different story. The genome of marsupials showed genes that were homologous to ZFY – thus, very similar sequences – on the other chromosomes, to the »sexual« ones.

Research into the chromosomes of four humans equally provided evidence against ZFY being TDF. Those four human subjects had developed testicles although they also had a »female« set of XX-chromosomes. Further research showed that they also had parts of the Y-chromosome in their genome. It may have gotten there through translocation during the formation of the gonads in the parental organisms. Yet, said translocation had not transmitted the ZFY-gene. On top of that, looking closer into the matter revealed sequences on the X-chromosome that was similar to ZFY ... In short, ZFY was ruled out as TDF. As a single gene it simply did not have the far-reaching importance of »switching on« the development of the testicles.

In 1990, the gene SRY was presented as yet another candidate for TDF. It is still considered the most important factor for the development of testicles, although it soon presented contradictory research results as well. SRY – short for »sex determining region Y« – is in itself another example for the androcentric perspective. It was not termed »testicle determining« but »sex determining« as it was deemed the crucial factor of turning the generally »female development« into the specifically »male« one if present.

SRY, just like ZFY, was believed to be on the short arm of the Y-chromosome again. In 1990, scientists could also prove the existence of an Sry-gene in a mouse that was homologous to a human one. Other mammals presented other homologues, although the sequence was only partially common to several species. Other mammals did not show SRY-genes at

all (or their correspondence), such as the Ryukyu spiny rat *(Tokudaia osimensis osimensis* and *spp.)* or the Transcaucasian mole vole *(Ellobius lutescens* and *tancrei)*. More baffling to proponents of SRY or TDF: those species did not even show *any chromosomic difference* between »female« and »male« individuals.

In its function, the SRY-protein may be a factor of transcription. It may be involved in a variety of processes affecting the development of testicles. Experiments with transgenic mice indicate such function (within limits, to be fair): mice with a »female« XX-set of chromosomes were provided with a DNA-sequence containing Sry. As a result, two of eight mice developed a »male« appearance and were infertile. Six of the mice presented a »female« appearance. Sry therefore may have had an effect on two of the eight mice. In experiments which infused human SRY in mice, they did not indicate any »masculinizing« effect at all. This in turn indicates (well, it was explained that way) the structural differences between human SRY and murine Sry.

Human subjects were studied who had a »male« XY-set of chromosomes but had only partially developed a »male« phenotype – their testicles were only partially functioning or non-functional at all. Ten to fifteen percent of them presented a variation of the SRY-gene. Human subjects with an »XX-set of chromosomes« and a complete or incomplete »male« appearance lacked SRY entirely. This was the case with eight percent of the former (those with a complete male appearance, three out of 39) and 91 percent of the latter (incomplete, 39 out of 43) (see Voß 2010: 250 et seq.).

Thus, SRY *may* play a role in the development of testicles. Yet, it cannot live up to the idea of being that one determining factor. Even biologists have come to terms with the idea – popular science still needs to catch up with the fact, though. Now, the quest has begun for other genes which may be set below or above SRY in *a system of assumed hierarchical levels* (thus, more or less important than SRY). Today, scientists even consider genes which may induce a »female« development.

Several other genes have been described which may affect the development of testicles below SRY. Let us not go into detail there because it would slow us down in our discussion of the matter of the »naturalness of sex.« Just a few important points may be presented (for a more detailed

discussion, see Voß 2010: 245 et seq. There is an overview of the currently researched genes as well as the progress that was made with them). Just as much:

1. There are contradictory results with these genes as there were with ZFY and SRY, although the other may not be as well-researched as those two.
2. It is important to keep in mind that much of the outcome of genetic research tells us something about the genome of mice, not necessarily humans. SRY/Sry has proved that findings for murine DNA *could* indicate to some degree an applicability for human DNA. They are not much more than hints at where to look for factors.
3. It is quite interesting and important that those other genes under scrutiny are *not* found in the »sexual chromosomes«, but rather those of the body in general: in particular, on the chromosomes 1, 3, 8, 9, 10 etc.
4. The effect of any gene (and these in particular) must not be understood like that of a light switch: they are not switched on in one development (say, the »female«) and switched off in the other (say, »male«). It is rather a matter of relation: when and how much is a gene »read«? It is a matter of *more and less*. In most cases of those genes under scrutiny, *that* specific gene at *that* specific point in time differs no more than by the factor four, three or two in subjects that are grouped as »female« or »male.« Seen individually, there are particularly interesting differences.
5. Candidates of genes which are believed to determine the sex are rarely confined to that development. They are always involved in the development of other organs and tissues such as, for instance, the heart, liver, or kidneys. Scientists rather frequently describe a gene's meaning for the development of the sex first and, almost like an afterthought, indicate that the »typically female« or »typically male« mouse embryos had perished in the womb or right after birth. Why? Because their hearts had not fully developed after scientists tempered with that »sexual gene.«
6. One last glimpse at the effect of SRY is as important as it is revealing. Gene SOX9, commonly found on the human chromosome 17, seems to be one of the genes which foster a »male« development

> even if SRY is absent. This does indicate that scientists may consider a hierarchical sequence of gene and their »products« that is *not unambiguous*. If seen like that, many genes (and their »products«) would interact in a complex and variable fashion in the development of the sex. The effect one gene has most likely could be compensated by others. Then, the question arises (following Evelyn Fox Keller): how is a certain stability maintained despite – or even *by* – individually varying processes when developing a functional heart or a sufficient organ of reproduction in the development of the sex?

Several genes which are assigned some significance in the development of the sex are currently understood as expressed (»read«). They precede SRY in the process and act – seen hierarchically – upstream of SRY. Their effect is seen, among others, in the first differentiation in the tissue of the genital tract and the formation of the undifferentiated gonads. All of those candidates (genes that influence the development of sex) are situated on other chromosomes than the »sexual« ones.

SF1 (steroidogenic factor 1) and its products is one of the candidates. SF1 is researched the best and located on the short arm of chromosome 9. The other is WT1 (Wilm's tumor 1 gene) which typically shows up on the short arm of chromosome 11. The expression of SF1 was recognized in the developing Leydig cell (they are important for the budding testicles), in the follicular epithelial cells, the theca cells, and the corpus luteim of the development of the ovaries. On top of that, we find them in parts of the hypothalamus, skin cells and the spleen.

We see Sf1 (the murine equivalent to the human SF1) act in mice differently according to sex. At a later point of the embryonic development there is a different expression in chromosomally identified »female« mice than there is in »male one.« While the expression of Sf1 in mice with a XX-set of chromosomes temporarily regressed, that in XY-embryos continued uninterrupted. Scientists concluded the influence of Sf1 in the development of the testicles. Although results are not exactly clear there, the same is assumed for human individuals.

The current research for WT1 is quite telling for the following discussion. Scientists present the products of Wt1 (mouse) and WT1 (human) as important regulators of Sry/SRY. The following genes may also interact

with Sry/SRY as factors of transcription: Wnt4/WNT4, Dax1/DAX1, Sox9/SOX9 and Amh/AMH. When Wt1 was absent, the embryos developed irregular kidneys, hearts, lungs, spleen and adrenal glands. Typically, those embryonic mice died in the womb or soon after birth. An altered WT1 especially leads to an irregular formation of kidneys in humans, it seems.

Most interesting is the fact that »reading« of one gene does not necessarily mean just one product is formed in the cell (a lesson Wt1/WT1 teaches us). Today, scientists know more than two dozen different forms of WT1-proteins. They are grouped into four main groups – and the different variants apparently have different functions in the organism. They already affect the formation of the sex differently. So, *one and the same gene leads to a variety of proteins.* How that may happen and what implications may it have is something to be seen. Just as much: scientists see two forms of the WT1 protein as especially important. It looks like the quantitative relation of both forms plays a role in the formation of the genital tract.

In 1986, the path breaking work of Eva M. Eicher and Linda L. Washburn shed new light on the development of the ovaries, too. Since then, it is not understood as »just happening« anymore. Scientists have begun to look for regulating factors, thus for »active« steps of development. As simple as it may sound: the authors have emphasized that ovaries are complex organs whose development requires a flow of signals. Again, scientists had subsequently tried to identify the »one gene switching on« the development of ovaries: ODF, the ovary determining factor. Again, just as TDF witnessed, several candidates were called to the podium, discussed, and eventually dismissed. The results were just too inconclusive. One »frontrunner« for ODF is absent as of today.

Several genes and their products were considered influential for the development of the ovaries. One of them should be mentioned briefly, as another interesting aspect is connected to it. The first gene described as a candidate for ODF was Dax1/DAX1 (dosage-sensitive sex reversal, adrenal hypoplasia congenital critical region on the X chromosome, gene 1, to be exact). It was identified after the search had been limited on an area of the X-chromosome for a while. DAX1 is typically situated on the short arm of the X-chromosome in the region of p21.3–p21.2. Its product, the DAX1-protein, supposedly acts as a factor of transcription.

One of Dax1's expressions could be identified in several embryonic tissues of mice: among others in the cerebral cortex, the spine, thymus, heart, lung, kidneys, ovaries and the testicles. Whereas the expression of Dax1 was temporally limited in mice with a »male« set of chromosomes (XY), it was identified in mice with a female set (XX) throughout the entire embryonic development.

The effect of Dax1/DAX1 is quite interesting: DAX1 was considered the opposite to SRY. Why? Humans with a »male« set of chromosomes (XY) developed ovaries, thus showed a »female« development, if the area of the DAX1 gene was present twice – in an additional copy. *It did not matter that the SRY-gene was also present and active*. This, of course, cast a doubt on the thesis of a »female« development in the absence of SRY.

What held true for the WT1-gene and -protein, also holds true here: there are variants of the DAX1-protein. One and the same gene leads to a variety of products which have an effect in the cells. It is a new and curious fact for the argument that DAX1 also demonstrates just how questionable a strictly binary division between »female« and »male« development might be. Apart from its influence over developing ovaries, DAX1 is currently assumed to equally play a role in developing fertile sperm cells of »male« individuals.

In essence, there might be some new understanding hidden in the research on a genetic level – if such research did not rest on the assumption of »male« or »female« developments. It is equally curious that to this point findings for the development of the genitalia are hardly considered for those of the gonads. Yet, as our discussion of the embryonic development demonstrated above, it seems clear just how connected and interdependent the formation of tissue and gonads are in the development of the genitalia.

Other genes, which are considered important for the development of the ovaries, are situated on different chromosomes than the »sexual« ones.

The essence of considering what biological-medical theories identified as the chromosomal and genetic factors of the sexual development is:

1. The search for determining factors moved from entire areas of the chromosomes to individual genes.
2. First, researchers stipulated one single factor inducing the development of testicles. From there, they later considered several or many factors which would take an effect successively or interactively.

3. There did develop, at last, an understanding for the complexity of a »female« development, just as there already was for a »male« one.
4. Genes are not the same as their products even if the latter do indeed have an effect on cells.

The following illustration *(figure 8)* represents one (!) model of how genes (and their products) may interact in a mouse – not because findings for mice may be transferrable onto humans. They are far from it, as already stated. There simply are no comparably complex representations available of such a model for humans.

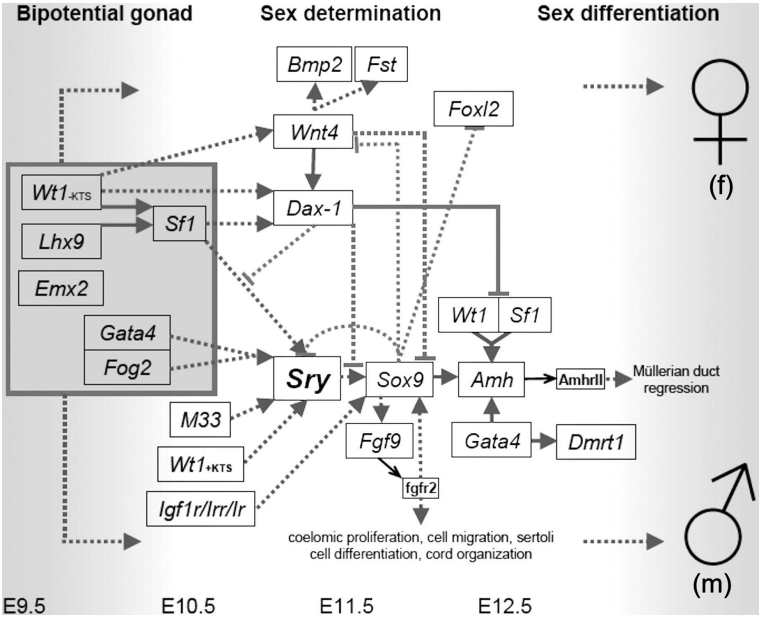


Figure 8: The interaction of genes and their products in the development of sex. The descriptions refer to mice and the time of their embryonic development (E) in days after fertilization (from 9.5 to 12.5). Arrow signify activating effects, the other connecting lines inhibiting ones. Solid lines indicate rather certain interaction; dotted lines indicate the indirect or assumed interaction. (f) = female development of sex; (m) = male development of sex (taken from Klattig 2006: 5).

Please do not feel intimidated by all the abbreviations for genes and their products. They are rather easy to access as are the detailed processes they are used to describe. The chart (figure 8) demonstrates well just *how many* factors seem involved in the development of the sex. We have already met some of them in our discussion above. Their interactions become clearer here. The analyses of gene expressions indicate that there might be some one thousand genes involved in the development of the sexes. When comparing those analyses, however, the candidates of what genes we are in fact talking about vary.

Consider the difference between the solid and the dotted lines in the chart. Whereas the first indicate the interaction between genes and their products we are rather certain of, the dotted ones refer to the assumed or indirect interaction. In other words, additional factors may play a role which researchers have not yet identified or fully understood. It is rather remarkable seeing the large number of dotted lines/assumed correlations and comparing them to the rather limited number of solid lines/certain identifications.

One certain conclusion, however, is rather simple: the idea of biology and medicine having access to a clear understanding of »what is going on« when sexes develop is no more than a phantasy – despite the fact that popular magazines foster that idea as do the German print media *Focus, Spiegel, Stern, Zeit*, or *Frankfurter Allgemeine Zeitung*. Our current biological-medical theories explaining the development of the sexes are far from being solid themselves – they are full of gaps. Scientists and researchers are aware of it (see Hiort 2007: 103). Yet, they also feel bound to simplification in order to inform the broader audience. Such simplification, by essence, has to level complexities in publications for the non-academic community. The complexities of the processes and the interaction of intertwined factors – in itself a necessary essence of our better understanding since about the early 1990s – fall short. The biological-medical sciences thus contribute to the stagnation of society's understanding of the genetic processes.

The outcome is (necessarily) rather simple. When being unaware of recent/current findings, »popular knowledge« *ideologically* remains on the grounds of the early twentieth century. Then, the far-reaching heredity of a multitude of characteristics was propagated and formed the basis for the biological racism and antisemitism. When considering the *genet-*

*ic processes*, popular knowledge does reflect the scientific understanding of the 1950s/1960s with their most basic models of how genes take an effect. In the end, such impermissible simplifications re-introduce those outdated theories into the biological and medical sciences themselves, because future scientists grow up with simple models, too.

## Development and Differentiation: The Transition to Process Orientation in Current Theories of the Development of the Sexes

As demonstrated, biology's understanding also broadens when it comes to theories of the development of the sexes. Now, the focus is not set on one gene or a limited number of genes anymore when describing the formation of the genitalia. The focus has shifted to a complex interaction: several genes and their products seem to interact in complex networks. Many factors to have an impact and the quantity of their expression do play a role. Then, »sound« research also has to consider that their complex interaction may result in more than two possible outcomes when the genital tract is formed. The interaction of a number of factors may rather lead to forms of the genital tract that are varied, different and are more or less capable of procreation. Or, seen differently, even when considering the similarities of the genitalia of two individuals it does not necessarily have to indicate the same path of development.

Our understanding of the complexity needs to expand even further: we have focused our considerations on the level of the »hereditary material«, the deoxyribonucleic acid (DNA). DNA, however, does not factually act independently within the cell. The cell itself regulates the required steps in the formation of the products which act in the cell. It is often a protein but it may also be an active product which is the result of an earlier step.

*As a first step, a »signal« induces* to »read« a certain area of the DNA. Such signal may be a »factor of transcription« we have met above. It may also be gradients of chemical molecules, a strong stimulation caused by heat, etc. Areas of DNA in the chromosomes which are not expressed are typically packed tightly – they are referred to as »chromatin.« In this

form, it is usually impossible to »read« the DNA, so the tight package needs to be loosened to allow the next step (transcription, *see below*) to take place. Accumulated chemical groups (here: »methylations«) may also play a role whether or not a DNA segment can be read. The chromatin structure is loosened by complex cellular processes.

Then, *transcription* may take place. It »transcribes« the DNA sequence into another, greater molecule which is also (just like DNA) a nucleic acid: ribonucleic acid, RNA. Both DNA and RNA are a long strand of succeeding »bases« which form the basis of the nucleic acids. Two specific bases always form one pair. Because they do, the specific base-pairing enables the formation of the RNA as a complementary (»inverted«) copy of the DNA sequence (called matrix then). This, too, is a complex process for which several factors have to interact. It regulates whether a transcription takes place, is initiated, elongated, or terminated.

Such transcription is not exactly one hundred percent accurate, if, for instance, a non-complementary base is included. »Repairing mechanisms« – again the result of many factors in the cell – ensures a certain accuracy (or inaccuracy). The outcome is a pre-mRNA (a not yet completed RNA-copy). There are further changes in the molecule after the transcription before a mature RNA exists. The pre-mRNA, for instance, receives a cap structure on one side which may vary from pre-mRNA to pre-mRNA. The »cap« may be necessary to stabilize the molecule for the transport from the cell nucleus to the cytoplasm and thus for further »translation« (discussed below).

On the other side of the pre-mRNA strand, *polyadenylation* takes place, meaning that some 200 adenin-nucleotides are added to the pre-mRNA without a matrix (adenine is one of the bases forming the DNA and RNA). The polyadenylation likely also effects the stability of the mature RNA strand. Some pre-mRNA, however, are not subjected to a polyadenylation.

The molecule is further altered through splicing/»cutting« individual areas from the RNA sequence. Although they were also the result of copying the matrix of the DNA, they may be cut as having no coding effect – in other words are not relevant for the subsequent product. As a side note, only two percent of the DNA itself are a coding sequence! The individual areas are spliced according to marker sequences – itself yet another complex process.

There is also the so-called »alternative splicing« which may result in cutting areas of the RNA which do have a coding effect. This may result in two *different* mature mRNA coming from two pre-mRNA with the *same* sequence of bases.

The resulting mRNA is then *transported from the nucleus to the cell plasm*. This transport, too, does not simply »happen.« It relies on a regulating process. Only there, in the cell plasm, can the mRNA be translated. Or, better, may be translated. It is not imperative as the mRNA may be broken down instead. The mRNA may survive for a few minutes only or for several hours – depending on its structure. During that period several translations may occur, only one, or none at all.

*Translation* – the process that re-writes the mRNA sequence into one of amino acids which in turn are the bases for the protein – rests on various factors again. This stage also depends on regulating factors determining whether translation takes place, is concluded, or terminated. The outcome is, as mentioned, the sequence of amino acids that forms the bases for the proteins – but, again, not yet a completed product affecting the cell. It depends on the *post translational* stage, chemical reactions leading to a product with a specific activity, reactivity and localization within the cell. Some specific segments of the amino acid sequence may be removed; others may be added anywhere within the sequence. Chemical groups – such as proteins, sugar or lipids – might be added or new chemical compounds integrated. *Only now does a particular product come into existence, with a defined special-geometric form that presents chemical and physical characteristics*.

Why did we look into the matter in such a detailed way? Well, one important point for the embryonic development might have become obvious: *DNA – or »genes« – are not blueprints which only require being carried out. They are rather the starting point of various processes in the cell that specifically react to the environmental influences from within the cell, the mother's organism or the environment in general. They determine the formation of the currently required information of a gene. From one gene (DNA) may result a number of various products which are then variously localized and also take various effects.*

Regulations take place on all levels, in other (and rather crude) words: the DNA of one flake of skin on the ground cannot develop into a full organism. The environmental conditions for the cell and the mother's

organism are crucial. The cells are not a mere (passive) depository of information but rather an (active) »reaction chamber« of multiple reactions that depend on the influences from the cell, the organism, and the environment. This »reaction chamber« and the influences having an effect there, determine the specific products and their formation. DNA is but one ingredient for their existence in the end.

Let us look to history once again: the idea of the DNA determining everything is as wrong (and disproved) as all the other theories of preformation. DNA is rather *one* of the involved factors within the cell. It is the cellular processes that extract the DNA's specific information when needed at a specific point in time. Those cellular factors – including various proteins – must come together and interact in order to form a specific, »required« product out of a DNA sequence.

Researcher have looked into such integrated, systemic considerations, of course. Yet, geneticists have also dominated the understanding by focusing on the DNA – piling upon it the conception of already harboring all necessary information for the formation of an organism. That information allegedly only requires being read.

The theories of Goldschmidt and Kammerer prove that the integrated, systemic approach is not new. Since the 1940s, such considerations have been known as »epigenetics« (not to be confused with epigenesist, described above). Conrad Hall Waddington (1905–75) from the 1940s onward had discussed as »epigenetics« the factors contributing to the implementation of the genes' information within the cell plasm. He saw genes as dominant factor, no doubt, but relying on the other parts of the cells for which he called for further research.

Today, such considerations might play a larger role, and the dominant position of the DNA might be called into question – rightfully so. »Epigenetics« might include considerations of how other chemical changes are involved in the re-formation of the chromatin structure, transcription and translation. Factors that originate in the mother's organism should also be considered, but also how nutrition and stress affect the outcome. The latter are currently assigned a rather dominant sway over the processes of (physical) development.

»Epigenetics« have become a known and noticed topic from about 2000 onward. Special issues of professional journals have done justice

to epigenetics. Yet, their articles have also limited the definition of the field again. There, the *multitude* of the processes in the cell and from the organism and environment are apparently not considered anymore. »Epigenetics« is rather limited to *some* factors that have *a direct effect on the DNA*. The focus has limited to some changes on the level of packing the DNA to chromatin and some chemical groups (or other factors) that foster or hinder the transcription of the DNA.

There are many factors involved in processes that are open for regulation. It leads us to a »lack of molds« for the development of the sexes. There is no strict and simple pattern of turning an organism into »female« or »male.« The genital tract is rather the outcome of the individual conditions and the impact of influences. There should be no doubt left that there are thus many forms of genital tracts possible. They do exist, but are, of course, mostly covered by clothes and therefore rarely move into the focus of biology – likely for the better. Individuals who do attract the physicians' attention for not fitting into the current standards of »female« or »male« are still often pressed into a clear visual appearance of being »female« and »male.« This is often achieved in an utterly inconsiderate and violent fashion (as in the case of intersexuality, see 1-0-1 intersex 2005, Völling 2010; Klöppel 2010). Those individuals may also constantly hear (and eventually accept) that they are »sick« as they may not reproduce or do not possess the »typical« sets of chromosomes or hormone levels.

Yet, when considering the multitude of factors which take part in the development of the sexes: what is typical, then? Is it the set of chromosomes that matters? Is it individual genes and the many products formed from them? What needs to be the quantity of a product that makes a human person »female« or »male«? The indicator might be the gonads – or do they have to possess the ability to produce germ cells, too? Must a »man« be able to produce functional sperm cells? Must a »woman« be able to produce egg cells? Or must she also have the »inner genitalia« to develop an embryo and bring it to term? Or, most crudely, does the other appearance of the genitalia determine the »typical«: in particular, the penis, testicles, and vagina? *Not one human individual will ever profess to all these characteristics at the same time. Thus, there will never be a »clear« direction towards »female« or »male.«*

## Conclusions

The theories of preformation (but also the natural-philosophical and biological-medical theories of the sexes) saw the existence of two sexes and their inequality in society. Theories from the end of the eighteenth century onwards dismissed them for explaining the factual possibilities of variations. This was achieved against the backdrop of more recent philosophical and considerable social changes, but also new »findings« of the natural scientist. Epigenesis with its developmental approach offered greater margins, now. That approach also allowed to explain the differences of the sexes – be it through the active progress or regress of the development. Yet, it equally allowed to explain the similarities between the sexes but also the woman-and-man-being of every individual.

The struggle between concepts of *preformation and development* has not seen a victor yet. Describing the structure of chromosomes and the DNA rather brought forth yet another wave of dominant preformistic theories. Only when they were identified as unsustainable did the perspective shift once more. Now researchers look into the interaction between factors, their being embedded within the cell and organisms, and the openness of developmental processes. In short, researchers look into a multitude of influences. *Thus, biology today arrives at systemic considerations in which development (epigenesist) rests at the core*. Biology witnessed new participants entering the debate: systems biology, theories of system organization, epigenetics ... Yet, they only have a slow impact on the theories of the sexes. When more complex research is done on the sexes, they often »rest« again (and again, dichotomously) on the social presupposition of two sexes: the sex of a »woman« and that of a »man.« Currently, epigenetics professes to that fact (see the essays of Bärbel Mauss and others, Mauss 2004).