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RECOLLECTIONS OF THE HEYDAY OF EXPERIMENTAL ENDOCRINOLOGY UNDER LAQUEUR AT THE AMSTERDAM POLDERWEG

By

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The Netherlands Society of Endocrinology has taken an initiative which needs no justification and scarcely any elucidation: its intention is to foster the living memory of the great *Ernst Laqueur* by the periodic organization of *Laqueur* lectures. Held as they will be by leading international figures in the world of experimental endocrinology they will doubtless be classics of strictly scientific exposition on current questions in endocrinology; their sights will be set high. They will be in honour of *Laqueur* but will no doubt fail to conjure up his spirit. Therefore it seems a fortunate idea to endow the first lecture in this series with a somewhat different character: as one of the few who today can still provide what one might call an eye-witness account, I want to take you back to the period of some twenty years, just before World War II: the heyday of experimental endocrinology at the Amsterdam Polderweg. For the main part I will do that with the help of disconnected recollections, without scientific pretensions; I shall strive to bring to life for you the Polderweg atmosphere rather than to give an accurate chronological account of all that was done and discovered. I will also set aside the contributions to pharmacology made by *Laqueur*'s group in that period, outside the hormonal field. If sometimes I use the pronoun »we« it is certainly not an imperial »we«, nor is it always to be taken literally but only as a matter of stylistic convenience.

The listener will do well to bear in mind the fact that science, and in

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particular its methodical-technical objectives, have evolved very rapidly in the last few decades, so that matters which were no less than revolutionary at that time will today perhaps strike you as primitive. The need for *quantitative* evidence to support tentative qualitative conclusions for example, nowadays commonplace, was stressed repeatedly by *Laqueur* in a period when it was far from being accepted as a matter-of-course. His argumentation – typical for the man – was of such simplicity that it has remained with me for more than 40 years. To demonstrate that qualitative data are only of importance where sufficient appropriate quantitative material is not available he took an analogy from common parlance »If my neighbour is broke except for his last sixpence, he's still got money,« he used to remark, »but when I say: »my neighbour has money« I mean something quite different.«

The realization of the significance of the quantitative element led him to pay especial attention to inter- and intra-individual differences in the sensitivity of test animals and to the development of reliable assay methods for every hormone that was studied under his supervision. Some of these (the assays for insulin and oestrone) penetrated as far as *Abderhalden*'s Handbook of Experimental Methods, and the *Heyl-Laqueur* unit for thyrotrophin has not been completely forgotten.

Deep was his despair whenever colleagues and particularly clinical colleagues proved unable to appreciate the implications of such problems. One famous German gynaecologist, after hearing from him a long account of the need for accuracy in the unitary assay of oestrogen preparations, replied that it was no doubt all very true »But dear Dr. *Laqueur,* please make them as strong as possible«.

Laqueur's interest in hormonal pharmacology was, as we were told in those days, aroused in an almost incidental fashion. In the period immediately following his appointment as professor, his laboratory was engaged primarily in a study of the chemo-therapeutic agents of the day, such as rivanol and tripaflavine. It was Dr. *van Os,* economy inspector for the city of Amsterdam, who drew his attention to the fact that in the large slaughterhouses vast quantities of animal organs were regarded and dealt with as refuse. In Mr. (later doctor *honoris causae*) *Saal van Zwanenberg,* Laqueur met a man who, like himelf, was ahead of his time. Both were aware of the vast therapeutic possibilities which could emerge. The N. V. Organon was established with as its original objective the preparation of therapeutically active organ extracts on a scientific foundation; there arose a form of co-operation between university and industry which at that time was highly unusual, but the advantages of which do not nowadays need to be stressed. Those concerned were however exposed at the time to frequent and fierce criticism which they refuted rightly and with great strength of mind.

It was understandable that the core of the joint effort was first directed

Professor Ernst Laqueur

to the question of *insulin*, then just discovered. It proved by no means simple to imitate the preparative method described by *Banting* and *Best*, even on a laboratory scale. Insulin was more or less rediscovered in *Laqueur*'s laboratory, and with Organon's support an apparatus was devised with which a somewhat purified product, suitable for use in man, could be produced on a small scale. Once this had been achieved the installation was moved to Oss as a matter of course. Thus the Netherlands were after Canada the first country to realize the industrial preparation of insulin.

Laqueur's main ambition in this and in similar situations was always to attain a satisfactory and if possible complete purification of a product intended for use in man. Even those who were at that time members of his staff hardly realized how much moral courage was necessary to maintain this objective resolutely in the face of such an utter lack of prior experience. His entire driving force, his talent for organization and his persuasive power in obtaining the necessary financial support was directed to this goal, and it was of a special satisfaction to him that, as far as insulin is concerned, it was fully achieved thanks to the efforts of Dr. *Dingemanse*.

The work of this eminent woman runs like a golden thread through the following period of fruition. She achieved almost the same measure of success with oestrone (or as it was at that time called Menformon) and other sub-

stances, and her achievements with respect to the differential determination of steroids in urine are still well remembered. Let us, however, not attempt to attach the names of individuals to all these various findings and discoveries, but recall instead the talent which *Laqueur* exhibited in the selection of collaborators who were subsequently to become world famous, among them *David, Freud, Kober* and naturally *Dingemanse.*

To return to insulin: Insulin was not only prepared and purified, but it was *further investigated* in numerous respects. To achieve a satisfactory purification a reliable assay was essential. As a criterion for this assay we could choose between the reduction of blood sugar levels and the induction of convulsions. In spite of the attractive simplicity of recording convulsions the effect on blood sugar was chosen as the basis for our assay method, firstly because it was more directly related to the therapeutic objective concerned and secondly (as one might expect from *Laqueur*) because it could be quantified. I still shudder if I think what might have happened if the other choice had been made. For since that time it has become quite apparent that the percentage of animals experiencing convulsions with a given degree of reduction of blood sugar levels decreases as the degree of purification of the insulin increases.

Had we assayed the fractions obtained during our purification efforts on their ability to produce convulsions, *Dingemanse*'s splendid final product would certainly never have been attained, although one's vision of a situation in which a pure convulsion-inducing substance would have been filled into ampoules and the insulin itself discarded is perhaps exaggerated.

A burning question relating to the assay was the following: in view of the considerable scatter of zero time blood sugar levels the assessment of any given insulin preparation with this method differed considerably according to the manner of interpretation of the figures obtained, i. e. whether these were interpreted absolutely, as percentages, or independent of the zero time recording on the basis of the lowest blood sugar level only. Fortunately our choice fell on the latter of these alternatives, although it must be admitted that during the years which followed an empiric statistical correction was introduced based on the initial blood sugar level.

Quite apart from assay problems many other points received attention, such as the treatment of hypoglycaemia with carbohydrates other than glucose, the influence of dietary factors on sensitivity to insulin, the possibility of routes of administration other than the usual one, the stability of the product under various physical conditions and such-like. It is difficult today to point to any particularly striking incident from this part of our study. The studies of the action of insulin on the other hand led to some intriguing situations. The hypothesis, understandable if one bears in mind the period at which it was advanced, was that an overdose of insulin might be expected to produce

signs and symptoms diametrically opposed to those found in the case of serious diabetics. In general this expectation proved to be fairly well justified, but when we observed that the intra-ocular pressure in rabbits receiving a toxic dose of insulin was actually *reduced*, exactly as observed in diabetic coma, we were faced with a seemingly inexplicable paradox. On further investigation this effect proved to be due not to a primary action of insulin, but to the accompanying muscular convulsion; the reduction in intra-ocular pressure could indeed be elicited with other convulsive agents too.

Furthermore it was found that the serum of animals in this condition itself possessed the ability to reduce intra-ocular pressure when given intravenously to other animals without inducing either convulsion or any fall in blood sugar. After a primitive method had been employed to remove all protein from such serum, a minor attempt was indeed made to use it for reduction of intra-ocular pressure in cases of glaucoma, but the study was abandoned when the preparations proved to produce a slight rise in temperature. Since, even at that time, the risk of occurrence of pyrogens in such preparations was not sufficiently appreciated, it is even today uncertain whether our intra-ocular hypotensive substance itself had pyrogenic activity.

One should also recall that our study of the dose-response curve of the very impure insulin available at that time led us to postulate the presence of a blood sugar *raising* substance in pancreas extracts, a quarter of a century before the actual discovery of Glucagon.

Let us now turn to the *oestrogens*. *Laqueur* was an opportunist in the best sense of the word; he was able to recognize and seize an opportunity wherever it presented itself. Hardly had the gynaecologist *Wijsenbeek* drawn his attention to the work of *Allen* and *Doisy* when he arranged to collect as much ovarium-follicle fluid as possible from adult mares. The oestrus test was introduced and quantified in our laboratory, and studies of extraction and purification were started. So it was that around 1925, almost simultaneous with *Loewe* and with *Zondek*, we had at our disposal active and protein-free oestrogen preparations. Today, now that the injection of all types of substances in oily solution has become usual, it seems remarkable that we made such strenuous and ingenious efforts to supply oestrone in aqueous solution. When this latter object was achieved with concentrations which, although low, were considered adequate at the time, the achievement of *Laqueur*'s group was truly the topic of the day.

The name Menformon, which was applied to the compound later to be known as oestrone, was introduced by *Laqueur* in anticipation of the significance which the substance was expected to possess for the menstrual cycle. The fact that oestrone indeed paved the way for menstrual bleeding, but that the latter only commenced after withdrawal of administration or the cessation of endogenous production, became known around 1930 (being published almost

simultaneously with the similar findings of *Maddeux* and of *Allen*) and it was a purely chance discovery. The female monkey *Pim* had been treated with oestrone for a considerable period and experienced bleeding only after the treatment had been abandoned because it was considered to have failed. During the preceding period of investigation, at which time we were still incorrectly under the illusion that we were facing failure, a German-speaking assistant delivered the following verse which pointed clearly to the doubt which we all experienced as to the capacity of oestrone in this respect.

Das Menformon ist kein Hormon,
Wie an Pim sich lässt demonstrieren.
Sie hat Liter davon im Leibe schon
Und will doch nicht menstruieren.*)

The chemical work, stimulated by the discoveries which had been made elsewhere regarding the occurrence of the substance in the placenta and in the urine of pregnant women and pregnant mares, proceeded apace and resulted in a completely successful purification, as recalled above; this was achieved independently of *Doisy* and of *Butenandt* who were the first to obtain crystals, although our achievement was a little later than theirs. We had slipped behind in the race because of our belief – a somewhat modest and pessimistic one – »that our product, although thoroughly purified would still not be compleely pure«; as a result of this belief we neglected to establish the crystalline condition at a sufficiently early stage. The purification studies also extended to such related substances as oestradiol, oestriol and equilin. In this respect one should recall not only the name of *Dingemanse,* but also of *Kober,* whose fame survived in the well-known *Kober* reaction for oestrogens. In addition a great deal of attention was paid to the chemical and physical stability of oestrone. In contrast to the experiences which we had had with insulin, the stability of oestrone proved to be surprisingly good, so much so that the persistent efforts which *Dingemanse* made to break down the compound reached the point where they had become monotonous for the rest of us. When oestrone was recovered glorious and intact after one very vicious attack, a member of the technical staff remarked »they might just as wel let a tram run over it now«.

As far as the biological work went, the initial efforts were devoted to improvement in the assay method, and in addition a search was made for effects other than the one employed by *Allen* and *Doisy,* which involved the in-

*) Is Menformon a Hormone? No!
(As Pim has demonstrated;
While litres through her tissues flow
She has still not menstruated)

duction of an oestrous condition in the vagina of a castrated female mouse. In this field, discoveries came in rapid succession. Within 2 years the growth effect on the female genitalia, the anti masculine effect and the anti ovarian effect had all been discovered and described, whilst the presence of a favourable effect on the nipple and mamma was also recognized. With regard to this latter, let me go into a little more detail. One must bear in mind that around 1927 endocrinologists were not merely unacquainted with the existence of prolactin, but that even progesterone was only known to them as a hypothetical »second female sex hormone«, considered to exist in the light of indirect evidence and arguments. We therefore attempted, so far as possible, to produce all the known signs of feminization in castrates with the use of oestrogens; when this failed, even with high doses, the effect concerned was simply attributed for the moment to the »corpus luteum hormone«, later to be known as progesterone. In view of subsequent events and in the light of our present knowledge it is remarkable to see to what extent oestrone was found to have effects on the mamma.

In spayed female guinea-pigs, which were the animals usually preferred for this test, experiments showed not only a growth effect on the nipple and the glandular tissue but also tended to show that after the withdrawal of treatment a true though limited measure of lactation, confirmed by chemical means, could occur. This secretion could be further promoted by suction, either using a pump or by the process of feeding the offspring. As we now realize, oestrone must have acted, though with he aid of prolactin, in the complete absence of progesterone! This artificial breakdown lactation (which one instinctively compares with the process of menstrual bleeding) could be prolonged artificially if oestrone administration was not abruptly withdrawn but was reduced in stages.

Exactly the same phenomenon could be produced in male cavia. Indeed, at a scientific meeting we were able to provide a demonstration stunt in the form of a new born guinea-pig which was being fed by its father, though admittedly the quantities of milk were small. The production of this effect in male animals was, however, not merely a form of scientific amusement. It provided the confirmation of a concept which had gradually developed in *Laqueur*'s school; this concept was essentially the independence of the *effect* of a sex hormone from the sex of the individual *subjects* exposed to its influence; the effect is determined by the presence of the necessary end organ even if in rudimentary form. Oestrogen cannot cause a uterus or vagina to develop in male animals but in those strains of mice which have a uterus masculinus (or more precisely a *vagina* masculinus) the latter can be brought into oestrus by administration of oestrone. The comb of a hen can for example, as was later shown, grow under influence of testosterone, but this compound cannot induce the development of a seminal vesicle, ductus deferens or any other

male organ in the female animal. This rule of thumb, which proved completely applicable to the hormonal studies on the mamma was confirmed in an unwelcome fashion in the clinic when the administration of testosterone to female subjects – for example in the treatment of carcinoma – was found to lead to vocal changes, hirsutism and growth of the clitoris.

The synthesis of »hormonoids«, with a more favourable ratio between their androgenic and anabolic effects, later provided a solution to this clinical poblem.

Returning now to the influence of oestrogen on the mamma; it should be pointed out that in view of the phenomenon which had been described one might have forecast that oestrone would inhibit lactation. That it indeed did so was known as early as 1930.

It was primarily as a result of a proposal from *Freud* that we started to administer oestrone to domestic poultry. *Freud* had been intrigued by the observation that castrated hens acquire male-type plumage. Oestrone proved indeed to induce the development of female plumage in cocks, capons and castrated hens. All this, taken along with the known fact that a male-type of plumage could develop even in the absence of the male gonads and thus of the male hormone, led to the interpretation of the »male plumage« in poultry as being in fact a neutral type of plumage developing when the quantities of oestrogen present were sufficiently low.

The more general hypothesis based on this concept is that in nature every sexual characteristic can occur in two forms, one of them being neutral and the other either male or female. The plumage can be neutral or female; the larynx can be neutral or male. This general hypothesis was not destined to develop into a firm rule. It suggested, in the above form, that *any* tissue involved in the development of sexual characteristics could only be influenced by the male hormone or the female hormone and that the effect of the one would not oppose the effect of the other. In a broad sense, and for many practical purposes this may be regarded as true, but there are certainly indications that the growth of the comb in poultry, such as is induced by testosterone can be hampered to some extent by oestrone. Similarly, the facial skin of a sexually mature woman is certainly much less well endowed with hair than that of a castrated man, even when such castration has taken place in childhood; in other words one must postulate some very minor forms of interference between the hormones associated with opposite sexes.

Indeed, even during the period of which I am speaking certain phenomenons came to light which, albeit in a different respect, were incompatible with the concept of a completely unilateral hormonal sensitivity of the tissues and organs comprising the reproductive system. I am thinking in this respect of the *paradoxical* effects of oestrogens: their ability to *enlarge* the sexual organs of castrated male animals. The first indications of such an effect were obtained

at approximately the same time in our laboratory as they were observed elsewhere by *Loewe* and *Lacassagne*, but the systematic studies of this subject took place in *Laqueur*'s laboratory. Roughly speaking, one is dealing here with an enlargement due solely to an increase in certain glandular elements: muscle connective tissue and (where present or where appearing as a result of metaplasia) squamous pavement epithelium. Testosterone, by contrast, brings about *balanced* growth and functional development of the entire organ. It is impossible, in the present account, to dwell in detail on the often surprising appearances which have been observed in the sexual organs of male animals after sub-chronic treatment with oestrone; the differences can be attributed to the varying praedilection of individual organs to such changes in different species. I will also pass over the speculations in the field of human pathology which found their origin in this work. Suffice it to say that the scientific importance of paradoxical effects continues to be stressed in present-day research.

Let me now recall two other discoveries from the period which we are discussing.

One of these concerned the possibility of preventing pregnancy in the rat with the aid of a high dose of oestrone some days after mating. This was attributed to an inhibition of nidation; later it was to be found that the actual effect involved was an interference with transport of the ovum to the uterus. At the time we considered it fortunate that this phenomenon was not observed in man. Veterinary surgeons, unhampered by moral, theological and similar considerations, have ever since that time made use of this method to restore the peace of mind of the owners of accidentally inseminated bitches.

As regards my other recollection I must unfortunately bring myself into the story since that will enable me to throw more light on the figure of *Freud,* who was the central personage. *Freud* had without any doubt a touch of genius, if one is prepared to apply that term to the ability to develop true inspiration without having available all the evidence which one would normally require for logical reasoning. One day he explained to me at length why in his opinion a carcinoma patient might be expected to have a raised oestrogen level in the blood.

I pointed out to him that his reasoning was based on faulty recollection; he had reversed or ignored a number of basic facts. After some reflection he admitted my point but he felt that we should at least test his hypothesis.

As I might have expected, knowing him as I did, he proved to be right. I have rarely experienced less satisfaction from a joint publication, and it was a meagre consolation to me to recall that the *Wassermann* reaction was equally the offspring of a faulty basic hypothesis.

Once the possibility of preparing oestrone-containing extracts from various starting materials began to come within sight, *Laqueur* naturally devoted some of his attention to the isolation of an analogous male hormone. The possibility

that there might be some chemical relationship, and hence some similarity as regards the appropriate solvents, means of extraction and suchlike was so evident that it was decided to apply the »menformon« technique to the male gonads and male urine. This soon led to the finding of *oestrone* in both these starting materials.

Disappointing though that may have been, it was at the same time a basically important observation, since it led at this early stage to a further realization that the distinction between and female was not an absolute one. It suggested the need to avoid the terms »male hormone« and »female hormone«, charged as they were with a measure of suggestion for which there was no adequate basis. Only by allowing this realization consistently to influence one's thinking in subsequent years was it possible to remain sufficiently unprejudiced to unravel, for example, the significance of the so-called »male hormone«, produced in the ovary, for the process of follicle maturation, instead of rejecting as absurd the first experimental findings tending to point in this direction. *At that time,* however, matters had not yet progressed so far. *Laqueur* was most certainly disappointed, but he did not despair. As always, he sought consolation in the quantitative element. Even larger quantities of urine and testes than hitherto were extracted and the assay method was once more critically reviewed and revised. From the very start, the easily visible growth of the capon comb had formed the criterion on which this assay was based. It was after all known that the comb, if untreated, remained small; the conclusion that the growth of the comb in the normal cock was due to the influence of testicular hormone was unassailable in the light of *Berthold*'s classic studies. In the early days, the height and breadth of the comb were directly measured in a primitive fashion. As a result of the work of the *Fremery*, a member of *Laqueur*'s staff, this technique was replaced by one employing a photographic record, the photographs being analysed planimetrically; later, the analysis was further improved using the selenium cell-technique.

And indeed, as early as 1929, i. e., very shortly after the observations of *Gallagher* and *Koch* and those of *Funk* had appeared, our first communication on active extracts of bull testis was published. On the other hand, both prior to this publication and later, a great deal of time was devoted to a preparation obtained from urine, the active component of which, androsterone, was later to be shown to be only a breakdown product of testosterone. The biological activity of androsterone showed a remarkable deficiency. Whereas the capon comb can apparently be sufficiently strongly influenced by this compound to develop as fully as that of the normal cock, androsterone proved incapable of masculinizing the internal genitals of castrated mammals.

In this connection, *Freud* made the striking observation that androsterone can indeed exert the latter effect when it is given in combination with oestrone, a phenomenon which he described as a »pace-make effect«. In the rat, for

example, this phenomenon can be most clearly demonstrated on the seminal vesicle. By virtue of the »paradoxical effect« mentioned earlier in the present paper, oestrone can enlarge this organ to a size many times greater than that in the untreated castrated animal, but the enlargement is confined to the muscular and connective tissue; the epithelium remains of the low cubical type and there is no sign of glandular development. Androsterone, which when given alone is virtually inactive, superimposes on the above changes the development of a high cylindrical, undulating epithelium, containing numerous glands which attain a secretory condition.

The same division of labour is observed with respect to the uterus, where closely analogous histological patterns develop in animals receiving oestrone with or without progesterone. Since *testosterone*, as is today firmly established, can lead *inter alia* to complete masculinization of a seminal vesicle, it combines in this respect the effects of oestrone and those of androsterone; it is therefore to be regarded as homologous to the combination of oestrone and progesterone, rather than to oestrone alone. The clarification of this point has been achieved thanks to the careful study of androsterone, a substance which itself has no therapeutic significance and must be regarded as nothing more than a urinary metabolite.

Once reliable and active preparations had become available, including those of testicular origin, it was possible to undertake a broad reassessment of the two concepts of the behaviour of sex hormones which had been developed earlier. If these were correct, it was argued, it should be possible to observe feminisation of the plumage under the influence of oestrone even where male hormone was given simultaneously to stimulate growth of the comb. And indeed we succeeded in eliciting just such a condition of *gynandromorphism* using this combination of injections. A very similar phenomenon is the simultaneous development of large nipples and a florid seminal vesicle which can be induced in castrated male guinea-pigs.

An apex of scientific achievement was attained around 1935 when *David* succeeded in isolating »true« testosterone from testicular material. A description of the somewhat depressing period of slow progress and intermittent failures which had preceded this discovery, and which might have led to an abandonment of our efforts had it not been for the indomitable optimism of *Laqueur*, is today of only limited interest. Let me merely recall an isolated incident from that period.

When *Laqueur* (in a paper, if I recall aright, to the Amsterdam Medical Society) presented with due pride his data on the successful isolation of testosterone, he stressed two points. One was the significance of a good quantitative assay, such as we had developed and applied in the form of the comb test. The other, as the reader will readily imagine, was the significance of the

quantity of starting material available, since the yield in the first successful experiment aiming at isolation was bound to be extremely minute.

He specified, raising his voice as he did so, the astronomical number of kilograms of bull testes which had been required to provide *David* with the opportunity to obtain a few pitiful milligrams of crystals. This was too much for one sceptic but insufficiently attentive listener. In the discussion he attested vehemently to his disbelief, based on his conviction that in the whole world there could not possibly be so many .... cocks.

This grandiose peak in *Laqueur*'s career might form a suitable topic, from the rhetorical point of view, with which to close the present historical account; any failure on my part to impart to you anything of the atmosphere of those days on the Polderweg would hardly be made good by a mere listing of the vast number of studies which were conducted with respect of thyroid, corpus-luteum hormone, the adrenal cortex, the epiphysis, the thymus and other organs. I must not, however, fail to recall the work performed on the pituitary hormones, in particular those of the anterior lobe.

Interest in this field had been aroused by *Zondek*'s remarkable finding as regards the gonadotrophic effect of a pituitary implant, and the further finding, shortly afterwards, that a gonadotrophic substance was present in the urine of pregnant women.

In view of the basic rule that the influence of a hormone can only be studied exactly in pharmacological tests when one starts with animals in a neutral condition, i. e. under circumstances in which the production of the hormone by the test animal itself can be entirely excluded, it was decided to introduce hypophysectomy as a routine method. The present generation of investigators will perhaps accept this statement without comment or surprise; at that time, however, it was a revolutionary and appallingly difficult undertaking. Many months of experimentation, involving the suspension of work in other fields, proved to be necessary, but the plan was carried through. It was one of the greaest achievements of *Freud,* an investigator whose many qualities included superb manual dexterity, that he successfully attained this end, developing a technique which could be imparted to members of the technical staff. From that time onwards we ordered hypophysectomized rats, as we ordered glassware, simply by placing an order with the laboratory assistant – a procedure which, for that time, was unusual in the extreme.

In order that the reader's patience shall not be unduly strained I shall pass over all the work that was performed with respect to thyrotrophic and corticotrophic hormones, growth hormone and prolactin, except for a few remarks on our work with gonadotrophins.

As early as 1930 it was known that the substance obtained from urine which was later to be known as »chorionic gonadotrophin« was also active *in the male animal,* though it did not induce any very considerable enlargement in the size

of the testes – a fact which appeared to conflict with the evidence of increased testosterone production, based on observations of the prostate, seminal vesicles and suchlike. In the testicles, however, despite their small size, there was a selective development of the Leydig cells, and the relationship between these two observations was correctly surmized.

Somewhat earlier, evidence had been obtained that *two* gonadotrophins were present in urine; this was based on variations in the relative incidence of oestrus and of corpus-luteum formation in female animals as between batches of »gonadotrophin« purified to different degrees.

Typical of the period was also the attempt, undertaken when no satisfactory preparations of progesterone were available, to demonstrate various effects of progesterone with the aid of gonadotrophin. Prolongation of pregnancy in rodents and the suppression of oestrus despite continuous exogenous administration of oestrone to intact female animals were attributed specifically to the action of the corpus luteum hormone. Whilst drawing this latter conclusion, we did not fall into the common error of interpreting oestrus suppression by progesterone as an anti-oestrogenic effect: The concept of »oestrus inhibition« is after all derived from the composition of the vaginal *smear*; the epithelial patterns observed in a *section* through the vaginal wall during true anoestrus and after administration of the combination of oestrone and progesterone are entirely different.

There was another, still common, error which *Laqueur*'s school consistently attempted to avoid, namely the concept that »a hormone is inhibited (or potentiated) by another substance«. It is never the hormone itself which is inhibited but its production (or its release at the site of production), or its effect. Carelessness in the use of language can lead to utter confusion, since these two types of effect occur at different endocrinological levels. Hence the name »story error«, which is sometimes applied to this fault; i. e. placing the phenomenon under discussion on the wrong story of the »Endocrine building«. It will be evident that a laboratory in which so many problems of current importance were in study at any one time throbbed with activity. It was not *Laqueur*'s nature to work and let us work quietly in a field free of other competition. The knowledge that the same discoveries were being prepared elsewhere in the world aroused his sporting instinct; for that reason, to use one of *Laqueur*'s own phrases, we were almost always working »under pressure«.

He complained himself, and he symphatised with us, about the intensity with which we had to work; his self-knowledge was perhaps insufficient to realize that without this element of urgency he was not in optimal form and could not feel thoroughly satisfied with his work.

Again with Organon's support he succeeded in building up a staff which for that time was relatively very large.

The laboratory, for all its limitations of size, sometimes had to provide space

for more than sixty workers. The scientific harvest which *Laqueur,* with all these collaborators – most of them hard-working investigators – was able to reap, was a large one, both quantitatively and qualitatively, and it is preserved in many hundreds of publications, each of which received his own personal attention.

All this made the utmost demands on his organizing talents and his capacity as a leader of men. It is true that he demanded the maximum of his staff, but they could in turn observe how the professor himself worked longer than any of his subordinates.

Laqueur, too, was always at hand when a member of his staff experienced personal difficulties. On such occasions the demanding master was suddenly conjured into a fatherly friend whose help, where necessary, was not confined to moral support alone.

The manner in which, and the extent to which, he took up the cause of refugees (in the fullest sense of the word) reflected this same fact of his character – his remarkable helpfulness.

So it was that the atmosphere in the laboratory was an extremely favourable one. It is difficult to define it precisely in words, but it survives as something of a »Polderweg complex« in the minds of all those who worked for a shorter or longer period. Any chance meeting with laboratory colleagues from those days still develops into a lively Polderweg-conversation, laced with a wealth of recollections and memories; workers from abroad – and there were many of them – fell equally under the spell of the place.

One of the latter, who after a period of study under *Dingemanse* had returned home and erected an installation for the separation of ketosteroids sent a snapshot of the latter with the caption »My own little Polderweg«.

The ability to attract and retain so many birds of different plumage, and to inspire them to the performance as a team of an integrated task was one of *Laqueur*'s most pronounced gifts. Later, when I was head of a much smaller laboratory elsewhere, I often wondered how he managed it. Seldom did he engage in actual teaching as such, yet we all learned a very great deal from him. He seldom praised a man explicitly, yet we were content to see how he observed and appreciated our achievements. In the course of a day's work he made little direct effort to render himself popular among his staff, and yet we look back to him with great affection and gratitude.

His influence on later research in the field of hormonal pharmacology in the Netherlands was to be tremendous. In Groningen, Leiden, Oss and Utrecht, scientific centres have come into being where this scienific discipline is exercised with great vigour. Of the endocrinological centre with *Laqueur* himself had set up in Amsterdam, few vestiges however remain. *Laqueur* had a strongly developed facility for objective discernment, and if he were alive today he might well have more understanding than others for the factors which have

led to this latter decline. The proverb about the prophet and his own country comes readily to mind.

That is one of the reasons why we have attempted, in this paper, to pay to his memory those honours which, in our view, were insufficiently bestowed upon it in his own city. If, here and there, we have done so in a light-hearted and even humorous manner, then we have only been following the example of *Laqueur* himself.

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