"The Rabbits are Prepared ..." - The Development of Ethinylestradiol and Ethinyltestosterone

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“The Rabbits are Prepared …” – The Development of Ethinylestradiol and Ethinyltestosterone

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In an exciting scientific neck-and-neck race, European and American scientists in the late 1920s and early 1930s isolated the ovarian, placental, and testicular hormones. At the same time the constitution of the human sex steroids was elucidated. However, it soon emerged that with oral administration the therapeutic value of the natural substances was extremely limited. The first-pass effect in the estrogens, the sensitivity of progestosterone to gastric acid, and the short plasma half-lives of natural ovarian hormones made treatment with them largely ineffective. The development by Hans Herloff Inhoffen and Walter Hohlweg of the orally effective sex steroids ethinylestradiol and ethinyltestosterone (ethisterone) in Berlin in 1937 can therefore be regarded as a milestone in the history of gynecological endocrinology. Ethinylestradiol is found even today as a highly effective estrogen component in almost all combined oral contraceptives. Ethinyltestosterone was the very first synthetic gestagen and can be regarded as the progenitor of the modern steroids in the 19-nortestosterone series. The present study describes details of the development of these two steroids and the history of their reception in the field of gynecology. In addition to the scientific literature, previously unpublished archival materials and German and American patent specifications were used in the study. The results show several surprising aspects, which are discussed in detail. J Reproduktionsmed Endokrinol 2011; 8 (Special Issue 1): 32–57.

Key words: history, endocrinology, steroids, ethinylestradiol, ethisterone, contraception

1 In the literature written in German, the English word “steroids” is often used. However, in the present work – above all in the case of the presentation of older investigations – the designation “Steroide” is also used. The subject under discussion is always the substance ethinylated in the 17α-position, formerly defined as 17α-ethynyl-1,3,5(10)-estratrien-3,17β-diol, but now defined as 19-Nor-17α-pregna-1,3,5(10)-trienn-20- yne-3,17-diol.

2 See reviews on the composition of oral contraceptives (e.g. the “Rote Liste”).


5 The company was founded by Ernst Schering (1824–1889) in North Berlin as a “Grüne Apotheke”. In 1855 he expanded the pharmacy laboratory into a works manufacturing chemical and pharmaceutical products. In 1871 it was converted to the “Chemische Fabrik auf die Fabrikation von Arzneimitteln”. In 1927 it was amalgamated with the “Chemische Fabrik CAF Kalibbaum GmbH” and the name of the company was changed to “Scherin KG Kalibbaum AG”. From 1937 the firm was called Schering AG. In 2006 the Schering AG was taken over by the Bayer AG, then named “Bayer Schering Pharma AG”. Since 2011 the trade name Schering has been abandoned for conversion to “Bayer HealthCare Pharmaceuticals”. Schering-Archive: www.wirtschaftsarchivportal.de/archiv/details/id/34. See in addition e.g., [Holländer H. Geschichte der Schering Aktiengesellschaft. Herausgegeben von der Schering AG Berlin. Gedruckt und verlegt bei Erich Blaschker, Berlin, 1955].
Appropriate publications in 1938 and 1939 made ethinylestradiol known to the professional world. However, years were still to pass before this estrogen could be introduced into therapy.

Hitherto, historians have not pointed out that examples of the preparation of the estrogen derivative are to be found in patents claimed by Schering AG in the years 1935 and 1936. In the corresponding patent specifications indications of the physiological action of the substance were given6.

Therefore the Schering chemists Arthur Serini, Lothar Strassberger and Josef Kathol seemed to be credited with invention of the process whereby ethinylestradiol was produced7.

The First Synthetic Gestagen

Closely coupled to their work on ethinylestradiol, Hohlweg and Inhoffen developed ethinyltestosterone8, the first synthetic preparation of a gestagen. Although this hormone derivative was used in therapy for just a few years, considered historically its appearance has tremendous importance. It is the precursor of a large group of artificial gestagens that can be delivered in tablet form, and which are at present indispensable for treatment with sexual hormones9.

The present paper describes in detail the discovery and reception of these two ethinyl compounds. Starting point are presentations of the patents and publications on the ethinylation of steroids, which preceded the work, now considered classic, of Hohlweg and Inhoffen. Thereafter reported on will be the publications of Hohlweg and Inhoffen, as well as the significant clinical investigations which led to the introduction into therapy of ethinylestradiol and ethinyltestosterone. Appropriate to its lasting practical importance, principal attention will then focus on the estrogen derivative.

The story of the discovery and reception of the two ethinyl steroids gives rise to many questions. For example, how do we account for the fact that processes for the production of ethinylestradiol were to be found in patents dated as early as 1935 and 1936? Why did it take so long for the estrogen derivative to be introduced into therapy? A discussion of these and other viewpoints occurs in the closing chapter.

For the present study original papers were viewed, so far as possible. This applies above all to chemical, physiological and clinical investigations directly linked to the ethinyl compounds. To discern the major relationships, however, general reviews had to be drawn upon, in which historical importance has not always been taken into account to a desirable extent. Many of the events under consideration are, moreover, dealt with only in part in a scientific fashion: even important questions of priority still await detailed analysis. This circumstance means that many questions remain unanswered.

Access to archives also presented problems. During the war years numerous documents were irrecoverably lost. This situation became painfully obvious during the attempt to obtain biographic information about the chemists working at Schering on research into the steroid hormones.

Synthesis, Biological Testing and Presentation of the Substance

On the Ethinylation of Steroids

By the mid-1930s the female gonadal hormones had been purified and their constitution elucidated. Joint efforts by biochemists, physiologists and medical men had led to the establishment of a rational therapy for numerous disturbances of the female hormone metabolism. The hormone preparations available for the treatment, however, left much to be desired, and for their isolation, enormous amounts of biological raw material were necessary. This made production complicated and expensive. Furthermore, it had become apparent that for physiological reasons there were strict limits to the oral use of estrogens10.

Progesterone could be administered only by injection.

With purification and elucidation of the constitution of the ovarian hormones, efforts to achieve partial or total syntheses of these substances had begun. At the same time ways were sought to achieve an increase in the hormonal activity by means of changes to the structure of the molecules of the estrogens. Through the discovery that the physiologically significant hormones of the supra-renal cortex belong to the steroids, research into the chemistry of this class of substances experienced enormous growth. Every effort to find simpler and cheaper ways of synthesizing these substances appeared justified. This – as will become apparent – would greatly benefit gynaecological endocrinology.

Within the framework of the efforts to obtain more effective estrogenic substances, by the mid-1930s various estrogenic acids had been prepared, besides the already mentioned benzoates of estrone and of estradiol. The significance of these compounds for the synthesis of ethinylestradiol and of ethinyltestosterone will be discussed later11.

The ethinylation of steroids, which was begun about 1935 and is the centre of interest in this discussion, initially served two objectives. On the one hand, the introduction of acetylene groups into certain steroids made possible the preparation of tertiary alcohols, from which it

6 See in addition pp. 34–7.
7 For biographical data see: p. 5, footnote (Serini) and p. 34, footnotes (Serini, Strassberger, Kathol).
8 The substance was first called “pregneninolon” by Hohlweg and Inhoffen because of its progesterone-like action. It was however – as became clear later – not a compound of the pregnane series, because the two carbon atoms of the ethinyl group at C17 are in the α-position. In ignorance of this circumstance, one also spoke of anhydrohydroxy-progesterone. Later the designation ethinyltestosterone or ethisterone (17α-hydroxy-pregna-4-en-20-yn-3-one) was adopted.
9 The discussion here is of the so-called 19-nor-steroids, which are testosterone derivatives, and which are demethylated at C10 (removal of C19) and carry an ethinyl group in the C-17α-position, as in the compound already prepared by Hohlweg and Inhoffen. The first of this group was developed by Djerassi and his colleagues at the beginning of the 50s, with norethisterone. See in addition [Fieser LF, Fieser M. Steroids. Reinhold Publishing Corporation, New York, Chapman and Hall, London, 1959, 951].
10 Here, only the estrogens occurring in women are considered. The so-called conjugated estrogens, that are obtained from the urine of pregnant mares, behave differently. They contain, inter alia, the equilins, that do not occur in women, and their metabolism is delayed. The first-pass effect thus does not play a great part. See in addition [Kuhl H, Taubert HD. Das Klimakterium. Pathophysiologie, Klinik, Therapie. Thieme-Verlag, Stuttgart, New York, 1987: p. 57 et 93].
11 See in addition p. 37.
Development of Ethinylestradiol and Ethinytestosterone

was hoped increased physiological activity would arise. On the other hand the ethinylated steroids would serve as starting materials for syntheses that would go further.

There are two sources of information as regards the early work on the ethinylation of steroids: the scientific literature and the patent specifications. The latter are gaining in importance for historiography, because investigations that lead to patents are not in every case published anywhere else. Drawing upon patents to clarify questions of priority proved, however, problematic, at least for the period before 1968. The reasons for this will be discussed in more detail later.

Here it must only be remembered that the description of a substance – in this case, ethinylestradiol – in a patent in the 1930s does not inevitably mean that at the date of the application it was actually already prepared. Worthy of protection at that time were processes only, but not the individual substances preparable thereby. Moreover then, as also today, during the years before the patent is granted, examples of synthesis can be subsequently filed.

The Early Patents

The patent in which a preparation of ethinylestradiol from estrone is described for the first time, was filed in 1935. It was granted to Schering AG in Berlin. Named as inventors of the “Process or the preparation of tertiary carbinols of the cyclopentanopolyhydrophenanthrene series” are Arthur Serini and Lothar Strassberger.

The application was dated 10th November, 1935 and the granting of the patent was made known on the 3rd December, 1942. As examples of the process, besides the preparation of ethinylestradiol, are cited four other syntheses with starting materials from the androstan series.

As the purpose of the process, the patent specification states very generally that the reaction products achieved should “[…] find use as such or as intermediates for the preparation of other physiologically valuable substances”. It goes on more specifically: “[…] e.g. substances with the effectiveness of masculine sex hormones to be transformed into such with the effectiveness of female sex hormones. In other cases […] the per oral effectiveness compared to the starting material will be considerably increased”.

The chemical details of the process described in the patent will be discussed here only insofar as they are of interest to the present work. Crucial is the fact that the tertiary alcohol group striven for by Serini and Strassberger was achieved, amongst other ways, by ethinylation of the keto group of steroids in position C17. Thus the inventors went from estrone to ethinylestradiol. This reaction appears in the patent specification also with the structural formulas.

The conversion of estrone requires parts of magnesium, phenyl bromide and ether to be gently boiled for 30h whilst acetylene is continuously passed through. Then estrone dissolved in ether is added. After 3 days the conversion products formed are hydrolysed the ketone that has not converted is removed and the end product is crystallised from methanol. The yield from their process, according to Serini and Strassberger, is 30%.

In the patent, details are given of the physiological importance of the ethinyl-estradiol thus prepared: “When administered subcutaneously it displays an activity that is equal to that of estradiol (1 RE = 0.1 γ) and in the case of oral administration its activity is considerably greater than that of estradiol (1 RE = 3 γ); ethinylestradiol 1 RE= 0.50 γ (!)”.

The second patent, which is dated before the classic publications of Hohlweg and Inhoffen and in which ethinylestradiol is described, was applied for on 22nd September, 1936. It likewise was granted to Schering AG and names as inventor Josef Kathol.

Almost analogously to the patent specification by Serini and Strassberger, the title is: “Process for the preparation of tertiary alcohols of the cyclopentanopolyhydrophenanthrene series”. The granting of the patent was disclosed on 14th September, 1939.

Specially noteworthy in this patent specification is that it gives two examples for the conversion to ethinyl-estradiol from estrone: one with a yield of only 3% and the second with a yield of over 90%. In this case the synthesis with the high yield does not correspond to the in all eight preceding examples of general process description. As will be apparent, it is much more a matter of a considerable modification.

Only Low Yield

In the first example, 1 g of “follicular hormone acetate” is dissolved in abso-

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12 See in addition pp 53–4.
13 See in addition commentaries on the Patent law, e.g. Molter 1936.
14 Arthur Serini (1897–1945). After his “Abitur” at the “Königliches Gymnasium” in Bonn (1915) Serini served in the army until 1918. Then he began the study of chemistry in Freiburg that he completed in Bonn in 1920. There he gained his doctorate with a paper “On the oxidation of pinacolin-hydrazone with mercury oxide” (Serini 1922). In the 1930s, he was one of the most productive members of the staff of the Schering main laboratory. He died in 1945, after the Russians entered Berlin.
15 Lothar Strassberger (b. 1902) gained his junior high school diploma at the “Oberealschule” in Würzburg in 1922. Then he studied chemistry at Würzburg University. In June 1927 he passed the final examination. In 1929 he was awarded his doctorate by the Philosophical Faculty of the University for a paper on the “Synthesis of syringin” [Strassberger L. Synthese des Syringins. Phil Diss Univ Würzburg 1929].
16 DRP 730 050, p. 3. The abbreviation RE means “Rattenheit” (rat unit). This is the smallest amount of an estrogenically active substance that is sufficient to trigger in a castrated rat the cyto logical changes in the vaginal epithelium that are typical of “estrus”. In the case of the last weight datum, a printing error has obviously been made. It ought to read: estradiol 1 RE 50γ; if one assumes this to be correct, then the values determined correspond exactly to those that Inhoffen and Hohlweg have given in their classic paper of 1938. See in addition p. 39.
17 Josef Kathol (b. 1899) after the “Abitur” at Easter 1918 enrolled at the Würzburg University to study mathematics. He was, however, immediately afterward called up for military service. After his discharge in March 1919 he began to study chemistry in Freiburg/Breisgau, which he completed in Würzburg in 1923. There in 1924 he was awarded his doctorate for a paper “On knowledge of the tertiary butyl group” [Kathol J. Zur Kenntnis der Tertiaäbutylgruppe. Phil Diss Univ Würzburg 1924]. After he joined Schering in the same year Kathol first worked on terpene chemistry. Later he worked in the Schering main laboratory on steroids. In 1936 he was transferred to manage the hormone operation in Adlershof. After the Adlershof works in East Germany had been expropriated in 1951, he worked in the patent department where in 1959 he obtained a power of attorney: Schering staff file.
18 DRP 681 869.
The processes presented in the two patents, in the outlined form, have apparently not been described in any scientific publication before 1937. Certainly, no references were found by looking through journals\textsuperscript{24} of those years, or consulting later publications on the ethinylation of steroids – with the exception of a footnote which will be discussed fully later, because it must be considered in connection with a claim for priority.

The US Patent of Inhoffen and Hohlweg

In contrast, that process for the ethinylation of estrone with a yield of more than 90% which is the highest yielding process given in the patent by Kathol, appears in a literal translation into English in a US patent granted to Inhoffen and Hohlweg in December, 1941. The patent specification carries the title “Tertiary alcohols of the estrone series and their derivatives and a process for their manufacture”\textsuperscript{25}.

The application was submitted in October, 1938. For the patent the priority of a German application on 25\textsuperscript{th} October, 1937 is claimed\textsuperscript{26}.

A comparison of the US patent with the cited patent specification by Kathol shows significant differences in the general process description which precedes the examples. Whereas in the patent by Hohlweg and Inhoffen it is expressly emphasised that the conversion of the starting material with potassium acetylide dissolved in liquid ammonia guarantees the best yield, as already mentioned, in the case of Kathol there is no hint of this. He describes this method merely as the last of his eight examples. Also, the very generally expressed patent claims by Kathol appear to be little matched to this special process – quite in contrast to the claims of Inhoffen and Hohlweg in the American patent, which is completely devoted to it\textsuperscript{27}.

In the literature, papers on the ethinylation of steroids first appear in the second half of 1937. Whereas in the presented patents the introduction of the tertiary alcohol at C17 is the primary interest, now the concentration is on the additional carbon atoms coupled there with the ethinyl group. In this way a possible way of adding side chains appeared to open, which was to provide a good practicable partial synthesis of difficultly accessible steroid hormones.

\section*{Papers of the Ruzicka Group}

The first of these publications\textsuperscript{28} was by the Swiss chemists Leopold Ruzicka\textsuperscript{29} and K. Hofmann. It carried the title “On the deposition of acetylene at the keto group in the C17 position in the case of trans-androsterone and $\Delta^4$-trans-dehydroandrosterone”\textsuperscript{30} and was submitted to

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ammonia. Ruzicka and Hofmann obtained by this means a yield of around 80%. They report nothing about the biological activity of their new compounds.

The results of this work are obviously part of a patent that was applied for by the „Gesellschaft für Chemische Industrie“ in Basel (CIBA) on 25th May, 193832. In it are taken into consideration several priorities from applications in Switzerland that go back to 26th June, 1937. The patent specification is entitled “Process for the preparation of acetylene derivatives of the cyclopentanopoly-hydrophenanthrene series”. In its contents it goes considerably beyond what is contained in the publication by Ruzicka and Hormann. In the introduction, earlier processes for the ethinylation of steroids are discussed33.

With reference to this it is stated that the yield had been only very small because a large part of the material resinified. References are not made to the extremely high yielding method described in the patent by Kathol as well as that by Inhoffen and Hohlweg.

No Statements about the Biological Activity
It is noteworthy that in the Swiss scientists’ patent the preparation of ethinyl-estradiol from estrone is described in the examples of the use of the process Ruzicka and Hofmann obtained ethinyl-estradiol with a yield of about 80%. In

32 DRP 702 063. An inventor is not named in the patent specification. There is much to suggest that Ruzicka and Hofmann were at least considerably involved in the patent specification. A corresponding US patent (no. 2 272 131) that was applied for in July, 1938 and which referred to an application in Switzerland in July, 1937, carried the name of Ruzicka.

33 References to sources are absent.


35 Willy Bernhard Logemann (b. 1909) passed his „Abitur“ in the “Humanistisches Gymnasium” in Oldenburg in 1928. Then he studied chemistry in Marburg. After the examination in 1934, he worked as “Liebig assistant” in the Chemical Institute of the University and received his doctorate in 1935 with a paper on “Investigations of the autoxidation of mercaptans. At the same time, a contribution to the chemical nature of papain” [Logemann W. Untersuchungen über die Autoxydation von Mercaptanen. Zugleich ein Beitrag zur chemischen Natur des Papains. Phil Diss Univ Marburg 1935]. Logemann, who at Schering worked successfully on steroids for many years, was the actual discoverer of the so-called “Serini reaction”, that played a part in the chemistry of the adrenal cortex steroids [Fieser LF, Fieser M. Steroids. Reinhold Publishing Corporation, New York, Chapman and Hall, London, 1959; p. 628]. It made possible the synthesis of deoxycorticosterone, that in 1939 was put on the market by Schering for the therapy of insufficiency of the adrenal cortex [Laurent H. 50 Jahre Steroidchemie bei Schering AG (1923–1973). Manuskript, datiert vom 24.5.1973 (beim Verfasser)].

36 Tadeus Reichstein (1897–1996) in 1929 became a docent and later Professor of Organic chemistry in the Federal Technische Hochschule in Zürich (ETH). From 1931 he worked as a personal assistant of Ruzicka, in 1938 he went to Basel. In 1932 Reichstein discovered the synthesis of Vitamin C and in 1936 the adrenal cortex hormone, corticosterone. In 1950 he received, together with the American biochemist Kendall and the rheumatologist Hench, the Nobel prize for medicine. See in addition: [Tausk M. Organon. The story of an unusual pharmaceutical enterprise. Published by Akzo Pharma bv, Oss, The Netherlands, 1984; pp. 6768].
added up to partial or complete satura-
tion37.  

Examples of ethinylation also given are the synthesis of Δ5-17-ethyl-
androsten-3,17-diol from dehydroepi-
androsterone and the preparation of 17-ethinylepiandrostan-3, 17-diol from
epiandrosterone. Report of further con-
versions is promised at a later date by
the authors.

In the paper the biological properties of the substances prepared are reported. The authors write, and this may be of particular physiological interest, “that the ethinyl compounds have the character of a female rather than a male hormone”. For example, the unit of the monoacetate of Δ5-17-ethyl-
androsten-3,17-diol in the Allen-Doisy test39 on the female rat was 0.2mg, whereas 1mg on the cockscomb was still ineffective39.

In contrast to Ruzicka and Hofmann, Kathol and his colleagues give no more extensive detail about the synthesis of the substances. They simply say that the attachment of the two carbon atoms takes place “by the use of the Nef reac-
tion”40, whereupon they refer to a large survey, but give no indication of the rel-
 vant pages. Data about the yields that were achieved in the ethinylations car-
rried out are likewise absent. No refer-
ence is to be found in the paper to the patents by Schering described in some detail above.

The absence of a full experimental sec-
tion in the publication by Kathol and his colleagues gives rise to the question as to which process was used by them. Hints are given in the footnote commented upon above, which relates to a paper by Inhoffen and Köster, in which was de-
scribed, in 1939, a new preparative pro-
cess for ethinylestosterone41. This says, in connection with the publications of the Swiss and Berlin groups: “The au-
thors of our working group are named in the first place, because their publication of a patent application, Dtsch. Reichs-
Pat. Anmeld. Sch. 111 452 IV c/120 of 21.11.1936 is the basis, whereas Ruzicka and colleagues published their first find-
ings on the same subject in October, 1937”. The cited application referred to the above patent presented by Kathol.

All Started with the Schering Patent
To sum up, it can be established that work had already been done in 1935 on the ethinylolation of steroids. The early in-
vestigations only found expression in patent specifications. They referred to the preparation of tertiary alcohols from compounds containing keto groups of the cyclopentanoperhydrophenanthrene series. It was hoped, by these alterations of steroids, to arrive at easily accessible substances that act as hormones.

Reports on ethinyl steroid compounds appeared in the scientific literature for the first time in October, 1937. Corre-
sponding publications, by the Swiss chemists Ruzicka and Hofmann and by the Schering chemists Kathol, Logemann and Serini, appeared almost simulta-
neously. In these the centre of interest was the side chain added with the aide of acetyleylene on C17: the endeavour was to achieve a partial synthesis of progester-
one and the hormones of the supra-renal cortex.

Various processes were used for the ethinylation. Initially, the yield was meagre. Very good results were first achieved when the condensation was completed in liquid ammonia by using the potassium salt of acetylene. The de-
scription of this method was first given in a Schering patent, applied for on 22nd November, 1936 and published on 3rd October, 1939.

In the early Schering patents (1935 and 1936) on acetylene addition on steroids, the preparation of ethinylestradiol had been described. In them were also given details of the physiological effect of this substance. From the present point of view this appears astonishing, because in the literature the discovery of the sub-
stance and its hormonal activity is al-
ways attributed to a paper by Inhoffen and Hohlweg in 1938. The possible causes for this contradiction (Fig. 4), briefly referred to in the introduction, will be discussed more fully later42.

How did the Synthesis of Ethin-
ylestradiol and Ethinylestos-
teron Come About?
The investigations, discussed above, into the ethinylolation of steroids by the groups of workers in Switzerland and in Berlin ended only a few weeks after their publica-
tion in the preparation of ethinylestradiol and ethinylestosterone. Both syntheses and the discovery of the bi-
ological activity of the substances are now – as mentioned – linked with the names of the chemists Walter Hohlweg and Hans Herlof Inhoffen. We shall now describe the circumstances that led to the work of Hohlweg and Inhoffen, the re-
 sults of which were first reported in the scientific literature in 1938.

In 1937, both Hohlweg and Inhoffen were working in the Berlin main labora-
tory of Schering AG. One of the tasks of the then 35-year old Austrian, Hohlweg, was the biological testing of all the hor-
monal derivatives developed by the company. In the course of his almost 10 years of work for Schering, Hohlweg’s main interest had shifted from pure chemistry to the physiology of the endocrine sys-
tem. Inhoffen was 31 years old and had worked in the main laboratory for just 1 year: in contrast, he worked exclusively in his original field.

There exist various descriptions by both scientists of the particular circumstances that at the end of 1937 first led to the preparation of ethinylestradiol. Essen-

38 The “Allen-Doisy-Test” determines the number of weight units of an estrogenic substance that is necessary to produce “estrus” in castrated rats. The “estrus” is manifested by the appearance of spe-
cific cornified epithelial cell forms in the vagina. “estrus” is manifested by the appearance of spe-
cific cornified epithelial cell forms in the vagina. In contrast to other bioassays, such as the “Cor-
ner-Allen test”, the “Allen-Doisy-test” retains its eponym even in its manifold variations.
39 The cockscomb test was used as a semiquan-
titative bioassay for the testing of substances for androgenic activity. It goes back to a paper by the American McGee. The criterion is the growth of the comb of a castrated animal that can be brought about by a certain amount of a hormonally active substance. Numerous modifications of the method were used. See in addition: [Bomskov C. Methodik der Hormonforschung. Bd. II. Thieme-Verlag, Leipzig, 1939: 445–76].
40 John Ulric Nef (1862–1915) [Nef JU. Ueber das eponym even in its manifold variations.
41 [Inhoffen HH, Köster H. Untersuchungen in der Sexualhormonreihe. IV. Mittel.: Ein neues Dar-
stellungsverfahren für Pregneninolon. Berichte der Deutschen Chemischen Gesellschaft 1939; 72: 595–6 (footnote 3)]
in the synthesis of equilenin acid.

Walter Hohlweg [...] came to me and immediately enthusiastic about this idea.

Of the ethinylestradiol thus prepared, he... 2 weeks. I add acetylene to the

The Great Surprise
Further biological experiments with ethinyltestosterone led, a little later, to another very surprising result, namely that the new substance displayed considerable progestogenic activity. In contrast to the highly purified progesterone then used in therapy, the new substance displayed its effect not only when injected but also when administered orally. Hohlweg... before the introduction of testosterone (dihydrotestosterone) into therapy, the substance was initially named pregneninolone.

It is not quite clear, from whom the decisive impulse came to test the ethinyltestosterone for progestogenic action. Schoeller wrote in a letter in 1955 that it had been him, “[...] that gave Hohlweg and Inhoffen the good advice, to test their ethinyltestosterone for corpus luteum activity, after they had told me, with great sadness, that the hoped-for masculine effect had failed to appear”.

In a lecture given by the manager of the main laboratory at the beginning of the 1940s, Hohlweg confirmed that Schoeller had spoken with him about the possible progestogenic activity of the ethinyltestosterone and that they considered appropriate tests. The suggestion arose when the close chemical relationship of the substance to progesterone was in mind. At that time Hohlweg had himself started the appropriate trials: “I [Hohlweg] could tell him [Schoeller] that the rabbits were already being prepared”.

The preparation and biological testing of the two ethinyl compounds were reported in several publications in 1938 and 1939. The details will be discussed later. The precise moment at which Hohlweg and Inhoffen for the first time held ethinylestradiol in their hands, can be established: it was 6th September, 1937.

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43 Hohlweg 1967 to Dr. Raspé, Schering AG. Scheringianum. Archive no. B1/266.

44 Walter Schoeller (1880–1965), after his “Abitur” in 1899, studied chemistry in Berlin. He prepared his dissertation under the famous chemist and professor Emil Fischer, who habilitated him in 1915. In 1919 Schoeller was given the title of Professor. In 1923 he joined Schering, where later as manager of the main laboratory he decisively influenced for decades the development of hormone research. On the importance of this scientist, see [Inhoffen HH. Walter Schoeller zum 80. Geburts- tag. Chemiker-Ztg–Chem Apparatur 1960; 84: 709–11].

45 “On the problems of the unpredictability of the paths from fundamental research to applied chemistry.” This is an account of a lecture that Inhoffen gave in 1983 at several universities. The manuscript was kindly entrusted to the author: Scheringianum, Archive no. B1/267.

46 Inhoffen 1983 (lecture).

47 Hohlweg 1967 (letter).

Starting point for the discovery of the two orally effective ethinyl steroids was thus the proposal by Hohlweg that 17-carboxylic estradiol should be made. For the historian this gives rise to the question, why the Austrian scientist hoped to get from this substance, what he, together with Inhoffen, discovered in ethinylestradiol.

The answer to this is to be found in a publication by Schering scientists (one of whom was Hohlweg) that appeared in 1971[53].

In this it states that the preparation of the 17-carboxylic estradiol was undertaken at that time because of the already known, good estrogenic activities of the estrogen acids. As examples, the authors cite doisynol acid and equinil acid[54]. Ethinylestradiol, however, pharmacologically surpassed all the synthetic estrogens known at the time, “[…] so that the estrogen acids and attempts to synthesize similar compounds were uninteresting”[55].

Horrible Efforts
In the cited work, it was a matter of an investigation in which the project that Hohlweg and Inhoffen had tackled in 1937, namely the preparation of the 17-carboxylic estradiol in a slightly modified form, had been brought to a successful completion. Decisive for this may well have been a suggestion by Hohlweg[56]. The 17α- and the 17β-estradiol acid were each made as its 3-methylether. In the process it appeared that, contrary to expectation, this synthesis was extremely difficult. Inhoffen, to whom the work was dedicated for his 60th birthday, spoke in this connection of “horrible efforts”[57]. Both substances proved also to be “nearly inactive” as estrogens[58].

In closing, it remains to be said that preparation of ethinylestosterone, shortly after Hohlweg and Inhoffen had achieved it, was also reported by Ruzicka’s group[59]. The Swiss scientists had, however, to recognize the priority of the Schering researchers. In contrast to the first publication by Hohlweg and Inhoffen, the paper by Ruzicka and his colleagues contains a detailed account of the method of preparation.

The Papers by Hohlweg and Inhoffen
Die Naturwissenschaften, 1938
The first publication on the synthesis of ethinylestradiol was in the journal Die Naturwissenschaften[60]. This was a brief initial communication, one page in length, under the heading “New orally effective female sex hormone derivatives: 17-ethinylestradiol and pregnen-in-3-ol-17”. The authors were Hans Herlof Inhoffen and Walter Hohlweg and the manuscript was dated 31st January, 1938.

Without going into details of the synthesis, the two Berlin scientists reported briefly on the preparation of ethinylestradiol from estrone. The synthesis of the substance was the result of efforts to make, from estrone, follicular hormone derivatives with good activity when administered orally. The observation had certainly been made in the past that, “there are connections between the chemical constitution and the strength of the activity when orally administered”[61].

Inhoffen and Hohlweg remark at this point, in a single sentence, that the new compound has shown no activity of the sort associated with a male sex hormone.

In closing, the publication says that if the new progesterin proves successful in clinical trials, it will be of great therapeutic importance, because a hormone hitherto only effective when injected could, in the future, be administered orally. The authors announce that more comprehen-

54 See in addition also [Hohlweg W, Inhoffen HH. Equileninsäure, ein oral hochwirksames Östrogen. Dtsch med Wchschr 1947; 72: 86–7].
56 Hohlweg 1967 (letter). He wrote: “Was an attempt ever made to make the estradiol acid that I wanted? As my new laboratories in Graz will soon be available and I have a capable chemist I would attempt the synthesis, if it has not already been done elsewhere”. Scheringsamml. Archive no. B 1/266.
57 Inhoffen 1983 (lecture).
60 [Inhoffen HH, Hohlweg W. Neue per os wirksame weibliche Keimdrüsenhormon-Derivate: 17-Aethinyloestriadiol und Pregnen-in-3-ol-17. Die Naturwissenschaften 1938; 26: 96].
61 Ibid, p. 96.
Development of Ethinylestradiol and Ethinyltestosterone

Figure 1. Hans Herloff Inhoffen. Source: Schering Archiv, Bayer AG.

Figure 2. Walter Hohlweg. Source: Schering Archiv, Bayer AG.

Figure 3. Walter Hohlweg (right side with chalk) in front of the formula for ethinyltestosterone [ethisterone]. Source: Schering Archiv, Bayer AG.

Figure 4. Inhoffen and Hohlweg’s classic publication in “Naturwissenschaften” 1938. The ethisterone was then still called pregnen-in-3-ol-17.

Figure 5. Advertisement for oral ethinyltestosterone from just after World War II. Source: Schering Archiv, Bayer AG.

Figure 6. Commercial packaging of ethinylestradiol (Progynon C). It arrived first on the German market in 1949. Source: Schering Archiv, Bayer AG.
Development of Ethinylestradiol and Ethinyltestosterone

The authors point out that the addition of acetylene on the 17th carbon atom of steroids from the androstane series, as discussed in the two cited papers, is pointed out as having been applied to estrone by Inhoffen and Hohlweg. By this means, the expected ethinylestradiol had been obtained. The melting point of the compound was 145–146°C.

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The authors point out that the addition of acetylene can lead to two isomers, the cis- and the trans-forms. However, the formation of only one of these isomers is very obviously strongly favoured, “since the product obtained at a 90% yield is undoubtedly uniform”66. To characterise the substance the monobenzoate, which crystallizes well, had been prepared, but after saponification with alkali it yielded the starting material with unaltered properties. This finding underlined the uniformity of the ethinyl compound.

Inhoffen and his co-authors then once again discuss the physiological activity of ethinylestradiol, that had previously been shown in the first publication by means of experiments with rats. Whereas then only comparisons of the subcutaneous and oral effectiveness of ethinylestradiol with those of the physiological gonadal hormones had been used, now additional substances are employed: it is a matter of the likewise ethinylated derivatives of equilin and equilenin67.

Supporting the fact of high oral effectiveness of ethinylestradiol (emphasized in the first paper), the authors go on to question the basis for this effect.

On this they say one has to assume, “[...] that the marked gastric and intestinal resorption that is apparent in the case of ethinyl compounds must be attributable to the presence of the ethinyl group”. To examine this assumption, the triple bond has been changed, by hydrogenation, to a double bond. Biological tests on rats by oral administration has then shown a decrease in activity of the substance (17-ethynylestradiol) to values that again correspond to those of estradiol. “The marked oral effectiveness of ethinylestradiol is thus in causal connection with the ethinyl group”68. Administered subcutaneously, ethinylestradiol has proved somewhat more active than even the ethinylated compound.

Inhoffen and colleagues then deal with ethinylestosterone, made in analogous fashion to the estrone derivative, that in the paper in Die Naturwissenschaften they had called pregnen-in-on-3-ol-17. They now call this compound pregnen-in-on-ol. This name is justified in a footnote by the statement that it is a matter of a derivative of pregnane, that in addition has the action of progesterone, and not that of testosterone69.

On the preparation of pregneninolone, it is stated one can start from ethinyl-androstenediol, which is obtained by addition of acetylene on dehydroandrosterone. The oxidation of the secondary alcohol group on C3 to a keto group finally leads to pregneninolone. The melting point of the compound is given as 264–266°C.

With regard to the progestin action of pregneninolone, the authors speak as in their first publication of the “very surprising results” of the biological test. Why the testosterone derivative for corpus luteum action had been investigated at all is not stated. On the topic of activity, Inhoffen and his co-authors again cite the published results of trials on baby rabbits pretreated with follicular hormone. In addition they say, “the ethinyl group in this compound, with a constitution very close to that of progesterone, thus leaves the subcutaneous activity essentially unchanged and, what is more, causes the appearance of an oral activity that the natural hormone lacks”70.

**Remarkably Effective**

In the case of pregneninolone also, the special relation between the ethinyl group and the physiological effect has been demonstrated. As in the case of ethinylestradiol, the appropriate ethinyl group had been obtained by partial hydrogenation of ethinyl androstendiol and subsequent oxidation of the oxy group on C3. The effective dose of pregnadien-ol-ons is 7.5 mg if administered subcutaneously, and 15mg if orally. The activity has thus decreased by about 1/4 when applied in both ways. The effectivity of the ethinyl derivative when administered orally, compares with progesterone strikingly: it is notably greater.

In the paper it is additionally pointed out that the progestin effect of pregneninolone disappears completely if one re-

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67 These substances, whose preparation is comprehensively described in the cited paper, will not be discussed in detail here. They remain unimportant.

68 [Inhoffen HH, Logemann W, Hohlweg W, Serini A. Untersuchungen in der Sexualhormon-Reihe. Berichte der Deutschen Chemischen Gesellschaft 1938; 71: 1025]. The assumption that the ethinyl group improves the resorption of the hormone in the gastric and intestinal tract, later proved to be false. The high oral activity is much more attributable to a delay of metabolism in the liver.

69 It was – however – as became clear later – not a compound of the pregnane series, because the two carbon atoms of the ethinyl group at C 17 are in the α-position.

It is noticeable in the presented paper that ethinylestradiol is practically no longer mentioned, although in the meantime a paper by Clauberg has appeared, in which clinical experiences with both ethinyl compounds are reported. The Berlin scientists mention the publication by Clauberg in only one sentence, saying that he had [...] been able to show the corpus luteum hormone action of pregneninolone in humans when orally administered [...]". Clauberg’s investigations will be reported comprehensively in connection with the history of the reception of ethinylestradiol.

Ethinylestradiol had Hardly a Role

Ethinylestradiol has scarcely played any part in later publications by


Hohlweg and Inhoffen. In a survey by Hohlweg of the oral activity of natural and synthetic estrogens, which appeared in 1950 in the *Wiener Klinische Wochenschrift*, the substance is mentioned only in passing. Of the synthetic estrogens, the author favours the use of dienestrol in the form of the diacetate, which is a stilbene derivative. Hohlweg referred to the results of clinical tests in the Universitäts-Frauenklinik der Charité, Berlin, where he was at the time head of the laboratory.

In detail the 1950 survey about ethinyl estradiol says: “Unfortunately, in the course of comprehensive clinical tests, this substance was not well tolerated. In the case of 20–30% of the women treated, nausea attacks occurred, similar to those which occur after treatment with stilbestrol. The preparation was therefore not initially introduced into therapy. During and after the war, however, it has been clinically tested abroad and because of its high activity it is used therapeutically, although its therapeutic range is relatively small”.

Only in his large contribution on “The hormones of the gonads” for the second edition of the handbook by Seitz-Amreich titled Biology and Pathology of the Woman that appeared in 1953, does Hohlweg state that ethinylestradiol had acquired “great therapeutic importance”. He does not refer here to the previously mentioned secondary effects, but emphasizes only that when administered orally to humans, the substance is 10 times as active as intramuscularly injected estradiol benzoate.

### On the Reception of the Ethinylsteroids

**First Clinical Tests in Germany**

As already mentioned, Inhoffen and Hohlweg reported in 1938 in their first publication on the preparation of the ethinyl compounds, that the clinical tests of the new substances had already begun. In the article published in *Die Naturwissenschaften* it is true that further details about the place and scope of the investigations are absent; in the later papers there are no references at all to clinical trials, either in progress or completed.

On looking through the literature, only one comprehensive publication (in 1938) is available on the action on the sex organs of women of orally used ethinylestradiol and progestrone and pregninolone. This paper deals with investigations by Clauberg, who at the time was senior consultant at the Universitäts-Frauenklinik at Königsberg in Prussia. Together with Ziya Üstün, a Turkish doctor at the hospital, Clauberg published the results relating to eight patients who had been treated with the new substance for secondary amenorrhoea, uterus hypoplasia and glandular-cystic hyperplasia of the endometrium. Clauberg’s paper will be comprehensively presented below.

### Buschbeck’s Investigations

In addition, Herbert Buschbeck, docent at the Universitäts-Frauenklinik Würzburg, reported on the first clinical experiences with ethinylestradiol and ethinyltestosterone. He did so during a lecture given to the Physical-Medical Association in Würzburg on 24th November, 1938. This lecture was reported in the *Klinische Wochenschrift* in 1939. Buschbeck’s own paper on this has not been found.

In the report, which is principally concerned with the orally effective estrogen stilbestrol, it is noted that 90 mg of ethinylestradiol, administered orally, “is sufficient to build up completely the mucous membrane”. Prevention of lactation was achieved with 24 mg, distributed over 4 days. When used for the treatment of dysmenorrhoea, amenorrhoea was observed for 2–3 months. In summarising it was stated: “The great activity when orally administered is very gratifying. The risks if inexpertly used are great. Schering AG are therefore for the present not putting the preparation on the market”.

Of progestrone and pregninolone, the reporter writes that this is the first “corpus luteum hormone” that is effective when orally administered. With 250–400 mg of the substance a secretory phase of the endometrium had been brought about. The preparation was harmless, and its use in cases of spastic dysmenorrhoea, emesis and hyperemesis gravidarum, as well as habitual abortions, was conceivable. Investigations of it must be continued.

### Treatment Trials at the Charité

Obviously at that time treatment trials with ethinylestradiol were also run at the Universitäts Frauenklinik at the Charité in Berlin. A corresponding reference is

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80 Literature is not cited here.
to be found in a paper by Hahn88, published in 1951, to which we will return later. According to the data given by this author, who at the time of the publication was an assistant physician at the hospital, treatment with the preparation was not introduced into therapy because of considerable side effects. The investigations mentioned have apparently not led to a publication. Hohlweg later indicated that it was Kaufmann who tested ethinylestradiol at the Charité89.

Until long after World War II, therefore, the paper by Clauberg remained in German-speaking countries the sole comprehensive publication concerned with the action of ethinylestradiol on women’s organs. For subsequent investigators – primarily scientists in the USA – it presented an important source on the clinical use of the substance and consequently was mentioned in almost all lists of references. In the case of pregneninolone, the situation was – as will be shown – somewhat different.

The Paper by Clauberg

Through the investigations by Clauberg and Üstün the information should be given, that an effective oral hormone therapy for women had become possible with the arrival of ethinylestradiol and pregneninolone. In the introduction to the paper it is noted that, of even the strongest of the hitherto usual follicular hormone preparations, when orally applied, at most a fifth of the amount of hormone introduced reaches the target organs to act upon them. In the case of the corpus luteum hormone, oral application had not been considered hitherto, because, as it was stated, the substance is immediately inactivated in the digestive tract.

The results of the investigations were published in August, 1938 in the Zentralblatt für Gynäkologie. The case history discloses that the treatments took place between February and May, 1938. The ethinylestradiol and pregneninolone were made available by Schering AG, and the substances carried the designations „Progynon C“ and „Proluton C“.

With the aid of hysterosalpingography and histology of the endometrium, Clauberg gave proof of the effectiveness of the orally administered preparations. Using X-ray presentation of the size of the uterine cavity both before and after completion of the hormone treatment, the growth of the womb could be established. On the endometrium the known histological criteria concerning the effect of the ovarian hormones were used.

As mentioned previously, the eight patients were women who came for therapy because of secondary amenorrhoea, primary sterility, or menstrual disturbances because of glandular-cystic hyperplasia of the endometrium. For the purposes of his investigation Clauberg formed three groups. In the first therapy was aimed at uterine growth, in the second at proliferation as well as transformation of a dormant endometrium and in the third group at the conversion of a hyperplastic mucous membrane into secretory transformation. With this division, three patients were found in both the first and the second group90. Thus in the framework of the same investigation were assessed the growth of the womb and the change of the uterine mucous membrane.

Of Special Interest: Secondary Amenorrhoea

The women were treated for very different periods (from 25 days to barely 3 months) with markedly differing doses of ethinylestradiol (EE) and pregneninolone. The considerations, by which Clauberg and Üstün allowed themselves to be guided, cannot be inferred from the paper. Also, the principle remains unmentioned according to which the histological examination of the endometrium in the various phases of the treatment was carried out. The authors merely briefly state that “the proof (of the effectiveness of both preparations) after oral administration was therefore here […] carried out in the same way as it had earlier been carried out by Clauberg for the injected preparations […]”91.

The third patient initially received 1 mg Progynon C per day over 10 days, and then 2 mg of estrogen daily for the next 10 days. The investigators then gave her 2 mg EE daily for a further 12 days, combined with, in all, 100 mg Proluton C (daily dose not stated). After 20 days of such therapy with estrogens, growth of the uterus was again ascertained, and after the 12th day of the combined treatment menstruation occurred, after a delay of 5 days. In this case a histological investigation of the endometrium was omitted.

90 Clauberg deviates here and elsewhere with the combined dose of estrogen/progestin in the second half of the cycle from the then widely used “Kaufmann scheme”.

[92 Clauberg deviates here and elsewhere with the combined dose of estrogen/progestin in the second half of the cycle from the then widely used “Kaufmann scheme”.
93 [Clauberg C, Üstün Z. Menstruation – per os erzeugt. Beweise der Wirksamkeit von Progynon C, einem neuen Follikelhormonderivat, und Proluton C, einem neuen Luteohormonpräparat, bei peroraler Verabreichung. Zbl Gynäkol 1938; 62: 1749.] At this place in the paper there is obviously an error in the dosage data. It says here, “[…] then from the 27th April to the 7th May, 1938 in all 30 mg Progynon C orally (twice daily, each of 5 mg) […]”. If one starts from the 10 mg per day, then the improbable total dose of 110 mg would be given for the last days of the therapy. Therefore 30 mg is assumed as a more probable value.
Optimal Dosage was of Little Interest

Looked at as a whole, Clauberg and his co-author appear to have regarded that proof of the oral effectiveness of the ethinyl compounds had been provided, in that the substances succeeded in producing growth of the uterus, menstruation and secretordial transformation of a hyperproliferated mucous membrane. The question of the optimal dosage was obviously of less interest. There were no indications as to why women with the same illness were given such different doses. The authors do not clearly explain the criteria according to which they determined the dosages.

As to the important question of the particular illnesses for which the ethinylestradiol should be given, the paper only says that one must in the case of oral administration reckon to use about 2–3 times the amount that is necessary in the case of intramuscular injection of follicular hormone. In reckoning the basis of the dose, Clauberg was bearing in mind the amount of generally used estradiol benzoate, that would achieve a good proliferation of the mucosa uteri. Furthermore, it was explained that there was no wish to establish a general standard for the orally administered dose.

Side-Effects not Mentioned

In the case of Proluton C the approach was somewhat different. Here the authors obviously started from the findings of Hohlweg and Inhoffen, which indicated that pregneninolone administered subcutaneously to a rabbit had about a third of the effectiveness of progesterone; if administered orally twice the dose was necessary. So Clauberg and Ústün reckoned with a factor of at least five to six when determining the transformation dose of pregneninolone for a woman. In the event at least 300 mg were finally given.

The omission of endometrium biopsies after combined estrogen/progesterin treatment was limited to the cases in which considerably less than the mentioned 300 mg of Proluton C had been administered. In these cases the investigators expected no transformation. This conclusion is supported by the statement of Clauberg, namely that the bleeding occurring in these cases is a consequence of the breakdown of mucous membrane in the proliferation because of a shortage of hormone.

Despite the enormously high doses (by today’s standards) that Clauberg and Ústün used in their estrogen treatment, no word is said of sideeffects. Furthermore, nothing is said of patients who had to be eliminated from the study at some stage because of intolerance of the medication. Finally, there is no evaluation with regard to the rank that the new substances could severally occupy in therapy.

The Introduction of Pregneninolone into Therapy

In contrast to ethinylestradiol, pregneninolone was introduced into therapy by Schering AG a very short time after its preparation. According to company documents, this first orally effective progesterin was put on the market in 1939. Primarily on account of wartime damage, archives are not now available which might indicate what preparations were involved and what the symptoms were for which the preparation was recommended.

In the “Rote Liste”, which provided information about medicaments that were on the market, the preparation first appeared under the name Proluton C in 1940. At that time the reference book was issued in an emergency format. In the brief entry there is no information about the chemical nature of the medication. It is merely characterised as a “corpus luteum preparation for oral administration”. Indications were habitual abortion and spastic dysmenorrhoea. The preparation was in the form of dragees each containing 5 or 10 mg of the active substance. The recommended dose was 1 or 2 dragees, 2 or 3 times per day.

Comprehensive information about Proluton C was contained in a scientific data sheet issued by Schering AG in 1955. In this it is noted, without reference to the introduction of the preparation, so long ago, that hitherto corpus luteum hormone could be administered only by injection, because enteral administration led to inactivation. By experiments which attempted to increase the oral effectiveness of gonadal hormones by introducing specific substituents, Inhoffen and Hohlweg had found in pregneninolone an “active substance very close to progesterone”, that even when administered orally was hardly less effective (Fig. 5; p. 40).

Secretory Transformation by Proluton C

The company then referred briefly to the results of experimental tests of the new substance. In the case of baby rabbits pretreated with follicular hormone, a secretory transformation of the mucous membrane of the uterus had been achievable with 4 mg of orally administered Proluton C. Pure progesterone had in contrast been ineffective even at a dosage of 60 mg. In the case of rabbits castrated after impregnation, Courrier and Fost had maintained the pregnancy by feeding with Proluton C.

In connection with the clinical testing of the preparation, reference is exclusively to Clauberg. He had succeeded, in women who had acquired an artificial mucous membrane by means of estrogens, in transforming by oral administration of pregneninolone the membrane into the secretory phase. After treatment with the progesterin, a genuine menstruation could be observed. Also a uterine mucous membrane, pathologically al-

96 Estradiol benzoate is distinguished by prolonged effectiveness. The endometrium build-up dose was 25–30 mg, distributed over five injections at intervals of 4 days. See in addition e.g. [Ufer J. Hormontherapie in der Frauenheilkunde. Grundlagen und Praxis. 5. Aufl., De Gruyter, Berlin-New York, 1978; 100].


98 [ibid., p. 1758.

99 The Berlin factories of Schering AG were almost completely destroyed by bombs and shelling in the last years of the war. In April 1945, the factories in Wedding, location of the main laboratory, were from time to time in the main fighting line. In May 1945, it was completely dismantled. See in addition [Holländer H. Geschichte der Schering Aktiengesellschaft. Herausgegeben von der Schering AG Berlin. Gedruckt und verlegt bei Erich Blaschaker, Berlin 1955; 70–3].


102 Literature references are missing.
tered in the sense of a glandular cystic hyperplasia, had been brought to physiological secretion. In this way a historically ensured corpus luteum hormone effect had been achieved for the first time by oral administration.

With regard to the necessary doses, it says in the information sheet that according to the investigations by Clauberg the sixfold amount of Proluton C orally administered is, in some cases, sufficient to achieve the same effect as injected progesterone. In general, however, as a basis for the dosage a ratio of 10:1 should be the starting point. Administered orally, 200–300 mg pregneninolone thus correspond to 25 mg of progesterone administered by injection.

The new preparation could be used in all complaints attributable to a deficiency of corpus luteum hormone. As important indications, the information sheet mentions habitual abortion, juvenile and climacteric bleeding as a consequence of glandular-cystic hyperplasia of the endometrium, as well as functional dysmenorrhea. Finally it says, Proluton C is excellently tolerated: side effects of any kind had never been observed.

**Great Therapeutic Range**

Although this Schering information sheet of 1955 for the clinical testing of ethinylestosterone referred only to Clauberg, at the time, however, the results of other investigations were also available. These investigations had been carried out in the early 1940s in Germany and abroad, and they will not be considered here because, by and large, they confirm the previously available results. Additional points were merely concerned with dosages considered necessary for the transformation of the endometrium. The question of ascertaining the dose, however, because of the great therapeutic range of pregneninolone, did not in the least play a role in the fundamental acceptance of the preparation. This compares not at all with the case of the investigations into ethinylestradiol, which will be discussed in detail later.

The Father of Modern Progestins

Rapid progress in steroid chemistry had already begun in the 40s, which served only to reduce the importance of the first synthetic progestin to historical interest. In 1940 the American chemist Russell E. Marker discovered a method by which the vegetable compound diosgenin could be converted to progesterone (and pregneninolone). This process was easily employed and could be based on an almost inexhaustible raw material source. Such raw material was accessible, however, only to the Allies during World War II. The availability of synthetic substances via the new process quickly led to a slump in the expensively priced natural hormone.

In 1944 the former assistant of Windaus isolated the vitamins, now classified as D1, D2 and D3. In 1928 he received a Nobel prize for his work on the constitution of the steroids and their relation to other natural substances. He discovered histamine and contributed to the synthesis of vitamin B1. [CDSB 1981: Concise Dictionary of Scientific Biography. Published under the auspices of the American Council of Learned Societies. Charles Scribner’s Sons, New York, 1981; 737.]

**Early Papers by American Authors on Ethinylestradiol**

Competition from the Stilbenes

After the publication of the much cited investigations by Clauberg and Üstün, nothing was at first said about ethinylestradiol. In the years 1939–1942 – as

104 Adolf Otto Reinhold Windaus (1876–1959); studied chemistry under Emil Fischer in Berlin and Heinrich Kiliani in Freiburg/Breisgau. From 1915 to 1945 Windaus was the Director of the Institute for Chemistry at Göttingen University. Windaus isolated the vitamins, now classified as D1, D2 and D3. In 1928 he received a Nobel prize for his work on the constitution of the steroids and their relation to other natural substances. He discovered histamine and contributed to the synthesis of vitamin B1. [CDSB 1981: Concise Dictionary of Scientific Biography. Published under the auspices of the American Council of Learned Societies. Charles Scribner’s Sons, New York, 1981; 737.]

105 Maximilian Ehrenstein (1889–1968) studied chemistry at Göttingen and from 1921 to 1923 was assistant to Windaus. In 1934 he emigrated to the USA. Previously he had acquired a doctorate in pharmaceutical chemistry at Berlin University. In 1949 Ehrenstein became Professor of Biochemistry at the University of Pennsylvania: [Straub H, Röder W (eds). International Biographical Dictionary of Central European Emigrés 1933–1944. Vol I and II. K. G. Saur, München-New York-London-Paris, 1983; 239.]


will be shown – few clinicians worked with the new substance, although interest in highly effective oral estrogen preparations steadily increased. This phenomenon, whose causes will be comprehensively discussed later, may be attributable to, inter alia, the discovery of diethylstilbestrol in 1938. This substance was the first and may well be the most important representative of a group of non-steroidal compounds with high estrogenic activity, an activity diminished when administration is oral. What is more, stilbestrol could be made easily and cheaply. Because of their importance for the reception of ethinylestradiol, the stilbenes will be discussed here in considerable detail.

The synthesis of diethylstilbestrol was achieved by the English biochemist Edward Charles Dodds and his colleagues after having worked on the problem for many years. It is not without interest to learn that Dodds obtained important, if not decisive, hints for his interest to learn that Dodds obtained important, if not decisive, hints for his work from Schering’s Berlin main laboratory. The new substance, because of its described properties, excited great interest amongst clinicians soon after its description in 1940 via a wealth of papers in the specialist literature. The question of the causes of this development will be considered later.

German Gynecologists were Reserved

Although intolerance phenomena similar to those experienced with overdoses of ethinylestradiol had been reported earlier, stilbestrol was widely used, above all in the USA, until the late 1960s. It was given in large doses of up to 300 mg per day for the treatment of impending abortion. In Germany the approach to the substance was considerably more reserved, primarily due to the influence of the gynaecologist Carl Kaufmann. This caution was to prove a blessing for at the beginning of the 1970s it became apparent that young girls whose mothers had been treated with stilbestrol during their pregnancies, consequently developed neoplasias of the vagina. The preparation is therefore no longer used in gynaecological therapy.

In the case of the few investigations of ethinylestradiol which at the end of the 1930s and beginning of the 1940s had been somewhat overshadowed by the stilbene derivatives, they were a matter of clinical studies by American authors. In Europe, then preoccupied by war, no one was intensively occupied with the steroids, although the paper by Clauberg had certainly created interest. The question of the causes of this development will be considered later.

Two Argentinians Made the Start

Probably the first foreign workers to become involved were the Argentinian gynaecologists J. A. Salaber and E. B. del Castillo who tested ethinylestradiol on three patients. The results of their investigations were published in January, 1939 in the journal published in Buenos Aires La Semana Medica. The indication for the therapy was, in all three cases, secondary amenorrhoea.

The patients were treated for 24, 29, or 32 days with a total dose between 7, 4 and 15 mg of the synthetic hormone. The authors reported that uterine bleeding had been started in all three patients, and in each case it occurred 4–6 days after medication ceased. Histological examination of the endometrium before and after the therapy did not take place. Salaber and del Castillo thus used a considerably smaller dose of ethinylestradiol than had Clauberg and Ustün. Considered as a whole, they reduced the daily dose by at least a factor of five. In their paper, in which they refer to Clauberg and Ustün as well as to Inhoffen and Hohlweg, this reduced dosage is specially emphasized. Justification for this is not given; all that is noted is that the therapeutic doses can be determined, only when a larger number of patients has been treated.

The two South Americans, in contrast to Clauberg, additionally reported on the toleration of the medication. The substance had been well tolerated. The effect was comparable with that of intra-muscularly injected estradiol monobenzoate. The authors were convinced that the use of ethinylestradiol would represent a real step forward in the field of hormone therapy for menstruation anomalies. The ethinylestradiol for their study was made available by the Schering subsidiary, Quimica Schering S.A. in Buenos Aires. It carried the designation “Neo-Estrona”.

Probably the first experiences of North American clinicians with ethinylestradiol were published by Robert Frank and his colleagues in 1940 in the journal Endocrinology. They considered the substance within the framework of a survey of newer preparations of sex hormones. The authors were members of a group of workers from the Endocrinology Clinic and the laboratories of the Mount Sinai Hospital in New York City.

The publication was concerned primarily – as one would expect at that time – with diethylstilbestrol. All that was said

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112 Edward Charles Dodds (1899–1973) was one of the most important English biochemists. He was Courtauld Professor at London University and Director of the Courtauld Institute of Biochemistry at the Middlesex Hospital. He received a life peerage in 1964. He was a Fellow of the Royal Society and President of the Royal College of Physicians as well as an honorary member of the American Association for cancer Research [Cancer Research 1983; 43: no. 9 (cover).]


114 See in addition Index Medicus 1938–1956.


117 No references can be found to publications that go beyond the already mentioned clinical tests at the Charité and the University of Würzburg.

118 [Salaber JA, del Castillo EB. Acción del etinilestradiol, derivado de la hormona follicular, por via oral. La semana medica 1939; 1: 6–10.]


120 [Frank RT, Goldberger MA, Felsen G. Clinical and laboratory investigations of some of the newer sex hormone preparations. Endocrinology 1940; 27: 381–4.] A preparation made by CIBA Pharmaceutical Products was tested. This company, like Roche-Organon and Schering in the USA made ethinylestradiol available for clinical investigations. The Schering corporation had, however, the major share of the clinical studies. The question as to why other firms had ethinyl estradiol at their disposal so soon after the discovery of this new substance, will be briefly discussed later.
about ethinylestradiol was that clinical tests of the substance had been broken off at a very early stage, because the majority of the patients after the first dose of the medicament had shown the most severe side-effects in the form of sickness and vomiting. Information about the indications and the doses is not given. The literature cited in the paper gives no indication as to which of the then available publications about ethinylestradiol had been consulted by the New York working group.

Despite these unencouraging results in therapy, the new substance was persisted with at the Mount Sinai Hospital. In the following year another team from the hospital (Udall J. Salmon and colleagues) published again about ethinylestradiol\(^{121}\). On this occasion the result of a clinical trial on 22 patients was described, all the patients having suffered from the menopause syndrome. Not a word was said about the treatments broken off because of the side-effects during the previous year.

The Ideal Drug: Low Dose, Cheap, Orally Applicable

The authors concentrated on explanation in detail of the importance of an orally effective estrogen for the therapy of climacteric complaints in particular. The treatment of the menopause syndrome requires a hormone substitute over a long period, it was said. The ideal preparation for the purpose must fulfill several conditions: high activity in small doses, simple administration by the patient herself, high tolerance and cheap manufacture. Salmon and his colleagues did not regard the preparations then available as capable of fulfilling these requirements in ideal fashion. Therefore ethinylestradiol was tested.

Among the 22 patients who were treated with ethinylestradiol tablets were some women castrated by surgery and others by radiation therapy. They all showed “[..] characteristic menopausal symptoms: hot flushes, nervousness, sleeplessness, gastrointestinal disturbances, vertigo, headaches and arthralgia”\(^{122}\).

The effect of the preparation was assessed by the degree to which these symptoms disappeared, but also by the estrogen effect on vaginal smears or by vaginal biopsy. Patients who cytologically or histologically showed no sign of hormone deficiency were not included in the study.

Salmon’s group of workers also used considerably smaller doses of the medicament than had Clauberg. Although the New York investigators expressly refer in their paper to the dosages used by the Königsberg doctor, it remains unexplained why they did not follow his suggestions. They also refrained from any comment on the explicitly ascertained fact that in Clauberg’s paper nothing was said about the side effects of ethinylestradiol.

Clear Estrogenic Effects

In the study by Salmon, at the start of the therapy the patients were first treated for 4–7 days with 1.8–3.15 mg of the preparation. The average daily dose was 0.45 mg. Within this period, with two exceptions, an improvement in the clinical symptoms was observable in all the women. In the vaginal mucous membrane, clear estrogenic effects were apparent. In the case of four women, the treatment had to be broken off because of sickness, vomiting and stomachaches, three further patients reacted to a dose decrease with improvement in the side-effects. After the initial phase, the treatment could be continued with daily doses between 0.15 and 0.3 mg. The authors report only one instance of uterine bleeding, which occurred 2 weeks after therapy ended, and this in the case of a patient who had received a total dose of 23.1 mg of ethinylestradiol over a period of 50 days.

In the assessment of their results the authors came to the conclusion that the tested substance orally administered in small doses shows high estrogenic activity. It therefore appeared to be extremely promising with regard to the above stated requirements for a substitution therapy in the climacterium. Before a recommendation for general use, however, the cause of the side-effects was to be elucidated in further investigations.

The study outlined above represented the prelude to numerous further investigations in the United States that finally, at the end of the 1940s, led to the introduction of ethinylestradiol into general therapy. Within the framework of this monograph it would be excessive to describe, in full detail and in chronological order, the studies that increased in numbers with the years. Representative of the whole collection therefore, will be exemplary investigations, which will be arranged according to the indications presented.

The Treatment of Ovarian Insufficiency

Therapy for the symptoms characteristic of the menopause, whether a consequence of natural or iatrogenic ovarian insufficiency, was clearly in the 1940s the principal occasion for further trials with ethinylestradiol. Besides women who suffered cessation phenomena due to age, patients were also treated whose ovaries, because of certain illnesses, had had to be removed surgically or whose ovaries had been made functionally inactive by irradiation.

The limitations that Salmon and his colleagues had placed in 1941 on the use of ethinylestradiol because of the observed side effects are not to be found in a paper published in 1942 by B. A. Watson\(^{123}\). Although the author, a worker in the Endocrinological Department of the sanatorium in Battle Creek, Michigan, did not use doses significantly smaller than those used by Salmon’s group, the undesirable reactions that occurred did not appear serious to him. “From our experience it is possible to conclude that ethinylestradiol is an effective and safe drug


\(^{122}\) Ibid, p. 556.

\(^{123}\) [Watson BA. Clinical experiences with oral ethinylestradiol. J Clin Endocr 1942; 2: 447–9.] Strange to say, at the start of the paper “ethinyl-estradiol benzoate” is spoken of as the tested substance. Later the author speaks only of “ethinyl-estradiol”. In the literature references he cites Clauberg 1938 and Salmon 1941, without pointing out a likely chemical difference of the tested substances. These two papers were the first on the clinical use of the new medicament, now also investigated by him, he explains (p. 447). Therefore it must be assumed that the designation “ethinylestradiol benzoate” is an error. [Clauberg C, Ustün Z. Menstruation – per os erzeugt. Be- weise der Wirksamkeit von Progynon C, einem neuen Follikelhormonderivat, und Prolution C, einem neuen Luteohormonpräparat, bei peroraler Verabreichung. Zbl Gynäkol 1938; 62: 1745–61, Salmon UJ, Geist SH, Walter RJ, Mintz N. Therapeutic effectiveness of orally administered ethinylestradiol. J Clin Endocrin 1941; 1: 556–8.]
to use in the treatment of menopausal symptoms […]," wrote Watson¹²⁴.

The investigation, published in the Journal of Clinical Endocrinology, was based on observations of 18 patients. The women were treated for several months, and they all suffered from typical menopausal phenomena, including hot flushes. "No patients were included in this study who did not experience flashes because it was felt that the disappearance of these would more clearly indicate subjective improvement", it is said in the paper¹²⁵.

**Successful Treatment with “Minimal Doses”**

Watson said concerning the doses that after some time a very specific scheme of application had proved especially favourable, because with it side-effects had been avoidable: three times 0.15 mg per day for the first 3 days, then reduction of the daily dose to 0.15 mg twice and finally, as long-term therapy, 0.15 mg ethinylestradiol daily. The treatment extended over 2 to 13 successive months. In the process only one failure of the therapy and one "toxic reaction" (urticaria) had been observed.

Morris J. Groper and Gerson A. Biskind reported on a successful treatment of the menopause syndrome with still smaller doses of ethinylestradiol ("minimal doses") in a paper that likewise appeared in 1942 in the Journal of Clinical Endocrinology¹²⁶. According to the experiences of these two authors, which were based on the treatment of 33 women, some over 2 years, the dose of the medicament could be reduced to 0.05 mg daily, without relapses of the patients.

It is apparent from the study that the treatment initially employed substantiably larger doses of the semi-synthetic estrogen. "When ethinylestradiol was first employed, the majority of patients was given 0.15 mg daily for a period of 14 to 21 days, and the dosage was then decreased to 0.15 mg every other day. In a few instances 0.30 mg was the initial daily dose and this was gradually decreased after 7 to 14 days"¹²⁷.

The principal concern of the investigation was the question of the effectiveness of the preparation in the control of the clinical symptoms associated with hormone deficiency. The estimation of the objectively detectable estrogen activity of the substance had been of secondary interest, wrote Groper and his co-author. In 27 out of 33 cases, first-class results in treatment had been achieved and a moderate improvement of the symptoms had occurred in two women. Only in four cases did failure of the therapy have to be admitted.

**Side-Effects Scarcely Occurred**

In the therapy described by Groper and Biskind, side-effects scarcely occurred. None of the treated women suffered from nausea or vomiting, the paper reports. Headache was observed in only three cases. Apart from one case, in which a termination of therapy was necessary, in other cases the symptom, despite continuation of the treatment, disappeared of its own accord. Consequently the comment is made: "The toxic manifestations that have been described with the nonsteroid oral estrogens did not occur." And in another place: "The development of an orally effective steroid estrogen […], which in our hands has shown practically no toxic symptoms, is a welcome advance"¹²⁸.

The therapy with ever smaller doses of ethinylestradiol was soon taken into account by the manufacturer. In the cited paper it is pointed out that after the administration of in all 0.85 mg over 17 days, on cessation of treatment bleeding had been recorded: in seven cases did failure of the therapy have to be recorded. Amongst the patients who previously had taken from 0.25 to 1.0 mg stilbestrol daily approximately were equally benefited by 0.05 mg ethinylestradiol." He also referred to the side-effects that Salmon and his colleagues had observed when giving larger doses of the medicament. The 0.05 mg ethinylestradiol per day that he had administered were well tolerated by 28 of the 30 patients. In one case there had been complaints about acute sickness, and in another the termination of the therapy had been necessary¹²⁹.

**“Excellent” Success**

The success of the treatment in 19 cases was rated by Soule as “excellent”; nine patients had responded well. One patient showed little or no improvement, so one case of complete therapeutic failure had to be recorded. Amongst the patients were 16 women whose hormone deficiency was the consequence of an operation. The problem of uterine bleeding after prolonged treatment with ethinylestradiol is not discussed in detail. Soule merely states that after the administration of in all 0.85 mg over 17 days, on cessation of treatment bleeding had been observable.

A recommendation for treatment interruptions is not given.

Since most of the patients in the study had been treated with other preparations before the ethinylestradiol therapy was started, the author had an opportunity to compare the subjective efficacies. Soule wrote in regard to this that "[…] twelve of the patients who previously had taken from 0.25 to 1.0 mg stilbestrol daily approximately were equally benefited by 0.05 mg ethinylestradiol.” He referred

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¹²⁴ Ibid, p. 449.
¹²⁵ Ibid, p. 447.
¹²⁷ Ibid, p. 703.
¹²⁸ Ibid, p. 706.

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The described small doses of ethinylestradiol were also successfully used, in the years after 1943, in other studies of the treatment of ovarian insufficiency. Floyd E. Harding reported in 1944 in the American Journal of Obstetrics and Gynecology that even daily doses of 0.02 mg of the substance had in certain cases produced a clear therapeutic success. As optimal daily doses for most patients with complaints in the natural or artificial postmenopause he indicated 0.05–0.1 mg of the estrogen derivative. He observed bleeding in women previously suffering from amenorrhea in 5 of 17 cases.

In another investigation in 1944 published by Robert A. Lyon at the Medical School of the University of California in San Francisco ethinylestradiol was used cyclically. The author reported on about 45 patients with the climacteric syndrome who had received daily doses of 0.05 mg for 21–24 days. This was followed by a treatment-free interval of 4 or 7 days. This scheme, so says the paper, should give the endometrium the possibility of regression or bleeding. The duration of the treatment-free interval was made dependent on how quickly the patients observed a recurrence of their complaints.

With Lower Dosage no Loss in Therapeutic Effect

Lyon summarized the results of his study, in which 348 cycles were investigated, to the result that the ethinyl compound made possible an effective therapy for the climacteric syndrome. Bleedings when the treatment was interrupted were not the rule, and in certain cases they could be avoided by further reductions of the dose, without a corresponding decrease in therapeutic effect. The undesirable side-effects that occurred were described by the author as “minimal and transitory.”

Hans Wiesbader and William Filler obtained similar results from an investigation of 53 patients with symptoms of ovarian insufficiency. In their study published in 1946, and also in the American Journal of Obstetrics and Gynecology, they also reported on biopsies of the endometria of 10 patients that were carried out before and during the therapy. These showed that when treated with 0.05 mg ethinylestradiol per day, after 14–20 days good proliferation of the mucosa was observable in each case.

Suppression of Lactation

As well as for the treatment of the postmenopausal syndrome, ethinylestradiol was used in early clinical trials in the USA to achieve the suppression of lactation during the puerperium. In the Journal of Clinical Endocrinology a group led by Lawrence Kurzrok reported in 1942 on the treatment of 59 women in childbed. In these cases daily doses up to 2.4 mg were used. The therapy in each case extended over 3–4 days.

Commenting on the results it is noted that at daily doses below 1.5 mg ethinylestradiol there were, relatively, many failures (9 out of 26 cases). If 1.5–2.4 mg were given, however, lactation would almost always be effectively suppressed (one failure). Side effects did not appear. The treatment was in most cases begun 1 or 2 days post partum; in one case, however, it was begun 8 weeks after birth.

In later publications, with a larger number of patients, the results were similar. Charles H. Birnberg for example, who belonged to Kurzrok’s group of workers in New York, published figures in 1947 for the successes in weaning with ethinylestradiol. In this publication, in which in addition other indications for the steroid hormone are discussed, it is said that effective suppression of lactation had been achieved in 75% of the 145 patients. In the case of these puerperae also, no side effects were observed. The doses used were, in all, 1.5 mg, distributed over 9 days.

Other Indications

In the USA after 1942 increasing numbers of other indications for the treatment with ethinylestradiol were tested. Thus Robert A. Lyon in 1943 reported in the journal Surgery, Gynecology and Obstetrics on the therapy of essential dysmenorrhea in the case of 12 patients. The plan of the treatment was based on observations, according to which this illness occurred only in ovulatory cycles. The administration of ethinylestradiol was seen to prevent ovulation and the formation of a corpus luteum.

For the study the author monitored, by means of basal temperature curves, a total of 138 cycles of his patients. In 44 of these cycles he treated for 21–24 days with 0.05 mg ethinyl steroid. In all cases, ovulation was suppressed and the occurrence of dysmenorrheic complaints was prevented. Lyon, however, pointed out in the paper that according to his and the experiences of others, this treatment could guarantee no permanent cure. The preparation had been tolerated well by all the patients.

In 1946, William Bickers reported (in the American Journal of Obstetrics and Gynecology) on the treatment of metrorrhagia with ethinylestradiol and progesterone. His 12 patients were younger women with strong and prolonged bleeding from proliferated endometrium with no occurrence of ovulation. The patients first received 0.3 mg

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130 Ibid, p. 316. The author here classes ethinyl-estradiol, in contrast to the stilbene derivates, as a natural estrogen.
of estrogen per day for 15 days, then on 5 further days the ethinylestradiol was combined in each case with 5 mg of progesterone administered by subcutaneous injection.

The paper records that, under the therapy the bleeding had stopped within 6 days (with just one exception). Menstrual bleeding began 5 days (at the most) after medication was interrupted. Bickers then continued in each case for two further cycles, whereby the administration of estrogen was begun always on the fifth day after the beginning of deprivation bleeding. In this way, in 90% of the women under treatment, a cyclic bleeding pattern had been induced. After completion of the treatment, 70% of the treated women retained the cycle, and in the case of half the patients ovulation had occurred (observation period 3–12 months).

The author pointed out that similar treatment trials had already been carried out in the past with stilbestrol. In these, however, incompatibility reactions had frequently forced the therapy to be stopped. In the treatment with ethinylestradiol in only one case had a small degree of nausea occurred. To sum up, it could be said that in the therapy of anovulatory bleeding, daily doses of 0.03 mg ethinylestradiol had been comparatively as effective as 5 mg diethylstilbestrol.

Therapy of Hypoplasias

In the paper by Birnberg and his colleagues cited above the treatment with ethinylestradiol of primary and secondary amenorrhea was also discussed. The therapy was undertaken in accordance with a uniform scheme (20 days each 0.05 mg ethinylestradiol, then a 10 day interval). The objective in the administration of estrogen was to start cyclic bleeding as well as to treat hypoplasias of uterus and mammae. The authors refrained from the administration of progestins, without giving a reason for this. The participants in the study were 24 patients aged from 16 to 35 years.

Concerning the results, it is recorded that in all these women periodic bleeding had

been accomplished, likewise it had been possible to achieve, in all cases of hypoplasia, a growth of the uterus and the cervix. In the case of the patients with primary amenorrhoea and slight development of the breasts (9 women), in the course of the therapy over several months a noteworthy growth of the breasts and nipples had been observable. Only two patients in the whole group had complained about slight sickness.

Towards the end of the 1940s ethinylestradiol was also used for induction of labour in pregnant women at term, in the case of missed abortion, acne, chronic haemospermia and in the therapy of carcinoma. In connection with the last-named indication, particular mention is made of prostate carcinoma and mammary carcinoma. These studies will however not be discussed in detail here.

In a survey of the literature on ethinylestradiol Kenneth Wade Thompson in 1948 wrote in the Journal of Clinical Endocrinology, that the substance had in the course of its testing clearly been proved to be the most effective oral estrogen. Its therapeutic effects were comparable to those of estradiol. The preparation was – after initial uncertainty about the dosage had been overcome – used successfully and without serious side-effects in all cases in which natural estrogens had proved useful.

The author, however, pointed out at the same time that further investigations of the metabolism of the substance in the human body were desirable. At that time scarcely anything was known about it.

The Introduction of Ethinylestradiol into Therapy by Schering (1949)

Ethinylestradiol was introduced into therapy by Schering in the Federal Republic of Germany in 1949, under the trade name Progynon C. In so doing, the company was relying primarily on the clinical experience with the substance in the USA. Recommended applications were initially in the area of climacteric complaints. The tablets put on the market each contained 0.02 mg of hormone (Fig. 6).

In a letter written by the company to doctors introducing the new preparation, it is stated that Progynon C has “[…] the great advantage of being orally fully effective, well tolerated and particularly economical.” With it the difficulties, that in the past arose because of the cost of a consistent hormone therapy, could be avoided.

With reference to the clinical investigations available by 1949, a first scientific information sheet from Schering about ethinylestradiol emphasized that the hormone possesses the same physiological effects as natural estradiol, namely, formation of the proliferation phase of the endometrium, growth of the uterus as well as influencing the secondary sex characteristics and the vaginal epithelium. Furthermore, for those reasons indications for the preparation, “are practically all branches of follicular hormone therapy.” Since initially the company had to hand only comprehensive results of clinical tests on symptoms of deficiency in the climacterium, the use of Progynon C was at first restricted to that area. As examples of complaints that could be treated with the preparation, the information sheet listed, besides the class hot flushes, vertigo, sleeplessness, depression, itchy skin eruptions, inflamed joints, circulatory disturbances and migraine.

Warning against Overdosage

In the advice concerning use, Schering expressly gave warning of the consequences of overdosing. Besides generally undesirable effects (such as headaches, dizziness and nausea) delays of menstrual periods, hypermenorrhoea, hyperplasia bleeding up to severe haemorrhages as well as painful swelling of the breasts could occur. It was rec-
ommended to begin the treatment of clima
teric complaints with one 0.02 mg
tablet 3 times a day, and once it began to
have an effect, slowly to reduce the dose
to one tablet a day or every other day in
severe cases or after castration an in-
crease of the daily amount of up to two
tablets three times a day was possible.

The initial limitation of the indication
for ethinylestradiol was soon abandoned
in following years, with increasing clini-
cal use of the substance in the Federal
Republic of Germany also. In combina-
tion with progestins the preparation later
served to bring on cyclic bleeding in
cases of primary and secondary amenor-
rhoea. Ovulatory bleeding and premen-
strual bleeding could be treated with
ethinylestradiol only. In addition, the
preparation found use at greater doses
for weaning, as a “Pille danach”, as well
as in the therapy of certain carcinomas.

The most Important Indication:
Contraception
The most important area of indication,
even today, for ethinylestradiol was
opened – as mentioned in the introduc-
tion to this monograph – at the end of the
1950s with the introduction of hormonal
contraceptive in the world, Schering in
1961 was the first pharmaceutical company in Europe to
put its own contraceptive pill Anovlar on
the market. Enovid contained as its es-
trogen component 150µg of mestranol,
the 3-methyl ether of 17α-ethinylestra-
diol, and 9.58 mg of norethynodrel. In
Anovlar there were used, in contrast,
50µg of the unetherified substance144
and 4mg of norethisterone – an estrogen
dose that already came very close to the
presently widely used 30 µg.

Thus ethinylestradiol had found a range of
application that is granted to very few
pharmaceutical products. Nothing has altered that, despite the fact that newer,
oraly easily used estrogen preparations have displaced ethinylestradiol for cer-
tain indications. The later developed de-
rivatives of the compound, such as
mestranol, that display hormonal activ-
ity after metabolism to ethinylestradiol,
scarcely still play a part. The future must
show whether other preparations can
displace ethinylestradiol in hormonal
contraceptives.

Discussion

If one regards the history of ethinylestra-
diol and ethinylestradiol in retro-
spect, the question that first arises is
where are the origins of the chemical
preparation of these two steroids. Al-
though details of the development of or-
ganic chemistry cannot be discussed at
this point, it should be established here
that papers by the American J. Nef
(1862–1915) and the Frenchman Victor
Grignard (1871–1935) provided deci-
sive pre-requisites. Nef contributed to
science the fundamental knowledge of
the ethinylation of aldehydes or ketones
with sodium acetylide to yield substi-
tuted alkinalins. Grignard later modified
this principle. Both procedures, respec-
tively known as the Nef and the Grignard
reactions, belong now to especially ef-
tective methods of synthesis in prepara-
tory chemistry145.

The discovery that liquid ammonia is an
excellent solvent and reagent goes back
to H. P. Cady (b. 1897) and E. C.
Franklin (1862–1937). They recognized
that this compound possesses properties
that are extremely similar to those of
water. Analogously to the aquo-system
of acids, bases and salts, Franklin after
1912 proposed a corresponding ammo-
noid system. Subsequently liquid ammo-
nia (NH) was increasingly used in syn-
theses as the solvent146. Decisive is the
ability of liquid ammonia to dissolve
alkali metals: they are then in a very
favourable form for organic reactions.

In the mid-30s, the steroid chemists in
their efforts to modify as well as to syn-
thetise these newly discovered sex hor-
mones could draw on these insights.
They thus already had available the tools
that made the preparation of the ethinyl-

144 See in addition [Schering AG (Hrsg). Die Pille
wird 20. So begann es . . . und da stehen wir heute.
Symposium, Berlin, 1981: 63.]
145 See in addition [Nef JU. Ueber das Phenylacety-
len, seine Salze und seine Halogensubstitutions-
produkte. Liebig’s Annalen der Chemie 1899; 307–
8: 264–328. Walden P. Geschichte der Organischen
Chemie seit 1880. Zweiter Band zu: Graebe C.
Geschichte der Organischen Chemie. Verlag von
Julius Springer, Berlin 1941. Reprint: Springer
Verlag, Berlin-Heidelberg-New York, [1972; 101–3.]]
146 Walden 1941, p. 111 et seq.

Development of Ethinylestradiol and Ethinyltestosterone

steroids possible. What follows will be
an attempt to honour the performances
of the scientists who directly or indi-
rectly participated in the development of
ethinylestradiol and ethinylestradiol
(ethinylestradiol). It is intended that the
analysis will relate to the synthesis as
well as the biological and clinical testing
of both substances. Particular impor-
tance in this case must be allotted to the
cited German patent specifications,
which appear to make questionable
Inhoffen’s claim for priority in the first
preparation of ethinylestradiol.

Problematic Location of
Sources
The first point to be mentioned is that
where there have been problems locating
sources, questions must remain unan-
swered. On many points, only probabili-
ties can be put forward. The problems
that arise in the discussion of the facts
presented in this monograph have in part
already been addressed. Essentially, it is
a matter of many documents having
been lost during the war. Also, in con-
nection with patents, access cannot be
had to official files. Only the patent
specifications still exist. The documents
that led to their drawing up and the infor-
mation about supplements that were sent
during the course of the patenting pro-
cess over many years have, in accor-
dance with the usual procedure, been
destroyed decades ago147. At Schering a
relevant exchange of letters with the
“Reichspatentamt” is likewise no longer
to be found.

It can be stated with certainty, that ste-
roids had been ethinylated already by
1935. The cited patent by the Schering
chemists, Serini and Strassberger, that
had been applied for on the 10th Novem-
ber, 1935, leaves no doubt about this,
since the corresponding process is the
subject of the patent claim. But what is
now the answer to the question, as to
whether ethinylestradiol had already
been prepared in 1935? Synthesis of the
substance at a yield of about 30% is
described in fourth place amongst the
five examples of the application in this
patent.

147 Information from the German Patent Office in
Munich.
Development of Ethinylestradiol and Ethinyltestosterone

Subsequent Filing of Examples was Usual
The patent law valid in those years, until the conclusion of the notification, allowed the subsequent filing of examples that could then be included in the patent specification. A complement of the patent by Serini and Strassberger with regard to the preparation specifically of ethinylestradiol was thus fundamentally possible up to 3rd December, 1942. The substance could therewith even after a first preparation at the end of 1937 by Inhoffen still be included in the already applied for patent as an additional example of the ethinylation of steroids containing keto groups. This likewise applies to the data ascertained by Hohlweg on the physiological effectiveness of the substance. In view of the protractedness of the then procedure for the granting of a patent, a sequence of events of this kind was entirely usual.

Several indications can be found in the available sources that in the patent by Serini and Strassberger, actual use was made of subsequent filing of process examples, and that ethinylestradiol was not contained in the original application. Thus for the development of the substance Schering later made payments to several chemists for participation in the invention. In contrast to Hohlweg, Inhoffen and some other chemists, Serini was not considered. Strassberger did indeed receive a share, though a relatively small one. It may, however, be assumed that these payments can be explained in relation to another contribution to steroid chemistry: identical payments went also to Hildebrandt and Logemann whose names appear in none of the patent specifications directly linked with ethinylestradiol.

Data from the Year 1937
A further indication of the subsequent filing of ethinylestradiol in the patent in question is presented by the data cited in the patent specification concerning the physiological effectiveness of the substance. These data correspond apart from one obvious misprint exactly to those that are cited in the classic paper by Hohlweg and Inhoffen from the year 1938. The data would in 1935, had they then been available, certainly have been considered as sensational as they were later. One would therefore scarcely have refrained from publication immediately after the patent application. Ethinylestradiol would thus have gone into clinical testing many years earlier.

In addition, Hohlweg has repeatedly emphasized that at the time in question, all newly prepared steroids were immediately subjected to a physiological test. The assumption that ethinylestradiol had possibly already been prepared in 1935, but not tested, is therefore scarcely probable.

More complicated is the situation of the cited patent filed by Kathol, that was applied for on 22nd November, 1936 and granted on 14th September, 1939. In connection with this, the author of the present monograph had to learn that limits are to be set to the theoretical consideration of scientific historical sources, disregard of which in some circumstances leads to false conclusions. The danger of false interpretations, as will be shown, is particularly great in the case of the theoretical analysis of old patent specifications.

In the patent by Kathol it happens as was pointed out that there are two processes for the preparation of ethinylestradiol, that differ enormously with regard to their efficiency. Whereas the first example of the synthesis (with a stated yield of just 3%) in principle corresponds to the other specified analogous ethinylation of substances from the androstane series, the last stated second possibility of preparing ethinylestradiol falls completely outside this framework. This second process makes use already of the elegant and particularly productive conversion in liquid ammonia, that was first described in the literature in 1937!

In this state of the sources it can be assumed that the conversion of estrone to ethinylestradiol in liquid ammonia in Kathol’s patent has likewise been subsequently filed. What, however, is the position of the synthesis example that is cited in the patent specification in the first place? With it could Kathol have succeeded in preparing ethinylestradiol before Inhoffen? Purely theoretically, this cannot be excluded. On the contrary, it even appears to give some clear hints of this.

Different Nomenclature
In the patent specification it is striking that Kathol uses a different nomenclature in the two examples of the preparation of ethinylestradiol. The first example, actually already revised in 1937, speaks of formulations of “follicle hormone” and “ethinyldihydrofollicular hormone”. The second, in contrast, refers to “estrone” and “17-ethinylestradiol-3,17”. This gives the impression that the first example must have been older and written before the papers by Inhoffen. Also the position of the two examples within the patent specification appears to support this view.

Rated still more significant could be the circumstance that Kathol, together with Inhoffen and Hohlweg, had received from Schering the largest inventor payment for the development of ethinylestradiol. In comparison to this, the already mentioned lower payments to several other company chemists are of secondary importance. Kathol’s contribution must have been of considerable importance.

That being so, explanation of the circumstance whereby ethinylestradiol was first subjected to a physiological test in 1937 caused difficulties, and Kathol plainly never claimed priority for the preparation of the substance. The former only appeared plausible, if it was assumed that Kathol had refrained from the physiological test because the small yield of his process given in the patent did not allow an economical utilization. The refraining from a claim of priority may be understood – admittedly unsatisfactorily – only as the consequence of a possible in-company agreement.

“Paper Example” not Reproducible
The foundation of all the considerations set out above was the assumption that the process, given in Kathol’s patent as the first example of the synthesis...
of ethinylestradiol, is actually practicable. This assumption has in retrospect proved to be wrong: in experiments that were carried out in the main laboratory of Schering AG in February, 1989, estrone acetate could be converted to ethinylestradiol only in vanishingly small amounts. Even with modern preparative and analytical procedures it was not very easy to isolate the small amount of ethinylestradiol from the (obtained) mixture of substances in pure crystalline form. At that time one had not been able to detect it analytically, to say nothing of isolating it, it says in the discussion of the corresponding experiments150.

Thus it can now be considered certain, that in the first process given by Kathol for the synthesis of ethinylestradiol it was a matter of a so-called “paper example”. Patent examples were labelled with this term when they were theoretically conceivable, though their practicability had never been closely investigated. They served to word a patent claim as widely as possible and thus to ensure advantages over the economic competition.

With regard to the Kathol patent, there are only two questions still unanswered. The first concerns the time at which the paper example was introduced. Here the use of the revised nomenclature justifies the assumption that it had already been a component of the original application. Final certainty could, however, be given only by the files, no longer existing, about the course of the patentgranting procedure. For the judging of the question of priority, this now appears pointless. The final clarification of this question would only be of weight for a discussion of the patent law situation in which Schering found itself at that time. In another connection, this will be briefly discussed later.

The second, still open, question is thrown up by the relatively large inventor’s payment received by Kathol in connection with the development of ethinylestradiol. For what contribution of the researcher was it made, if not for that patent example? Here too, only speculation is possible. It appears not improbable, however, that with the payment the company made remuneration for the development of the process for ethinylestradiol syntheses in patents applied for before 1937 do not, as at first appeared, affect Inhoffen’s priority for the preparation of this steroid. Two of these examples are of processes that, in accordance with the legal requirements in the course of the granting of a patent, had been subsequently filed. The third, in retrospect, turns out to be a “paper example” that is not practicable. This whole situation shows that the use of patent specifications for the clarification of questions of priority can be extremely problematic. It appears as a rule to be permissible only if the practicability of the processes described therein is proved to be beyond doubt.

**Consistent Continuation of Research**

In the case of the synthesis of ethinyltestosterone (ethisterone), there are from the very beginning no difficulties with regard to the question of priority. The preparation of the first artificial orally effective progestin by Inhoffen must be regarded as the result of consistent continuation of his and Hohlweg’s work on ethinylestradiol. This work was in turn based on the investigations of the Schering chemists Kathol, Logemann and Serini, who at about the same time as the Swiss chemists Ruzicka and Hofmann had developed an elegant method of ethinylating steroids with a yield of over 90%.

It has been fully outlined that ethinyltestosterone was actually only intended to be an intermediate in the synthesis of a 17-estradiol acid. There were no great hopes linked with this intermediate substance and it was a matter of surprise when it proved to be a highly effective estrogen. The estrogen acid aimed at, in contrast, could as was shown decades later in no way fulfill the expectations imposed on it. Ethinylestradiol, prepared analogously to ethinylestradiol, and conceived as a possible androgen, proved, likewise quite unexpectedly, to be an active progestin. The historian must here ask himself whether chance directed events rather than purposeful scientific deliberation.

Retrospective consideration of the outlined events shows clearly that as a result of the elucidation of the structure of estrogens, derivatives of these hormones with better therapeutic applicability were very purposefully sought. Furthermore, steroid chemists endeavoured to find ways of partially or completely synthesizing the laboriously accessible natural substances. Thus were first obtained the estrogen esters whose effect was protracted, and the estrogen acids in the course of well considered investigations. The cited efforts are those most closely linked with the names of Hohlweg, Inhoffen, Doisy and Butenandt.

**Several Factors were Decisive**

Immediately decisive in the discovery of ethinylestradiol were several factors: Hohlweg’s urging to prepare a 17-estradiol acid, the work of Kathol, Logemann and Serini on ethinylation and Inhoffen’s transfer of this reaction to estrone, as well as the physiological testing of the intermediate obtained, again by Hohlweg.

The importance of the preparatory work in Schering’s main laboratory on the ethinylation of steroids that finally ended in the productive process with the conversion in liquid ammonia, cannot be too highly esteemed. Without this decisive progress, Inhoffen would perhaps have sought for another way of synthesizing the desired estradiol acid, and the experimental test of ethinylestradiol on animals would not have been done for some time.

However, here it must also be pointed out that the elegant and productive ethinylation of steroids in liquid ammonia was to some extent “in the air” in 1937. Ruzicka and Hofmann discovered the process at least at the same time as the Schering chemists, if not before. It appears quite conceivable that Example

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150 The author thanks Dr.-Ing. Henry Laurent, the then manager of the Scientific Secretariat in the Institute for Medicament Chemistry of Schering AG, for the idea of testing Example 1 in Kathol’s patent for its practicability, and carrying out the corresponding experiment. Only in this way may a false interpretation of available sources be avoided. See in addition the experiment protocol in Frobenius 1990 (Appendix, p. 97).
8 was subsequently inserted in Kathol’s patent, because the method had previously been patented for Ruzicka or CIBA, and therefore could not be patented by Schering. Since the example also occurred in the claim of Kathol’s patent, it could be “saved” in this patent specification. Another application in which the example was originally contained must possibly have been withdrawn or was rejected; only the parallel application in the USA for Hohlweg and Inhoffen succeeded. This view of the matter is supported by the fact that a German patent corresponding to the US patent cannot be found, although in the US patent reference is made to a German application on 25th October, 1937.

The physiological test of ethinylestradiol itself can, quite simply, not be regarded as a product of chance. Hohlweg has repeatedly pointed out that in his laboratory all the substances produced by syntheses had to be tested for their hormonal activity. To this systematic procedure, to which Dohrn had already in the 1920s ascribed the greatest importance at Schering, many other successes of the company are due. The discovery resulting from the physiological test is accounted for in what Inhoffen (in his lecture) has called the “problem of the unpredictability of the paths from fundamental research to applied chemistry”.

From this aspect also is to be viewed the preparation of ethinyltestosterone and the discovery of its progestin effect. Here, obviously, considerations of the assumed structure of the molecule had already led to the correct path, after the originally expected androgen effect had not been detectable in experiments on animals.

First Tests in the Toxic Region
Finally, the circumstances should now be discussed which accompanied the introduction of ethinylestradiol into therapy. As was comprehensively shown after the first clinical test by Clauberg, it took more than 10 years before the substance was put on the market in the Federal Republic of Germany. In marked contrast to this, ethinyltestosterone had already been released for general medical use in 1939. Closer consideration of the course of the clinical trials of ethinylestradiol is a good example of what difficulties have to be overcome in the introduction of a highly effective new medication, and how decisive in this sort of case is the effect of systematic procedure.

An essential reason for the delayed introduction of ethinylestradiol is certainly to be found in the fact that the substance, when orally administered to human beings, displays such extreme estrogenic activity. The results of the tests on animals could give only an inadequate indication of this. Hohlweg’s investigations had indeed shown that in the Allen-Doisy test on rats, 3 μg of the substance, administered orally, were effective and thus ethinylestradiol exceeded the natural estrogens by a factor of 3 to 20. The actual potency of the medication in the treatment of women could, however, not be estimated from this.

For the reasons stated, the first clinical investigators used doses that in retrospect certainly were in the toxic region. The administered amounts of the estrone derivative as in the case of the natural estrogens, their esters and also stilbestrol were in the milligram region and must have triggered massive incompatibility phenomena. Relevant observations were then soon made and communicated by Buschbeck. It is, however, extremely remarkable that there is no mention of this problem in Clauberg’s paper of 1938. Other investigators were caused by the observed side effects to discontinue their studies at an early stage.

Thus the incompatibility phenomena consequent upon overdosing formed the most substantial hurdle that ethinylestradiol had to take on its triumphant advance towards the goal of being the therapeutically most used estrogen. The question now arises as to why so few efforts were made in Germany to help the preparation to overcome this obstacle. The present monograph shows that the foundations for its clinical use had been laid almost exclusively through investigations by American authors during the 1940s.

Chances Wrongly Estimated?
Here an important part was certainly played by World War II. Whereas at this time researchers among the American clinicians could continue their work comparatively unhindered, for their colleagues active in Germany, conditions became steadily worse: many of them were called up for military service, and the exchange of scientific information was limited as investigations important to the war effort and the basic care of patients had absolute priority. Furthermore, since 1933 the National Socialists had discriminated against numerous outstanding researchers because of their political attitude or their race, and had forced them to emigrate or had even killed them. Under these circumstances clinical studies of an estrogenic hormone could scarcely thrive.

When looking through the publications of Hohlweg and Inhoffen on the ethinyl compounds, however, the impression arises that the observed incompatibility phenomena in the first clinical tests of ethinylestradiol led the people in the Schering main laboratory too quickly to a pessimistic assessment of the future chances of the preparation. As an indication of this an instance may be taken which has already been referred to: in the publication about pregneninolone in the Klinische Wochenschrift of 1939 there is practically no longer any mention of ethinylestradiol, although its excellent effectiveness in women after Clauberg’s publication in 1938 must have been unquestionable. In 1950, Hohlweg himself still favoured a stilbene derivative amongst the estrogens that could be administered orally.

The reasons the Schering Corporation in the USA had for nevertheless making ethinylestradiol available for clinical trials, can only be speculated upon. Possibly the responsible staff in the American subsidiary viewed the preparation more optimistically. Perhaps they saw themselves induced to do so for competitive reasons, since ethinylestradiol was soon offered there by other companies (CIBA Pharmaceutical Products

152 Carl Kaufmann for example, who never made a secret of his rejection of National Socialism and therefore got into great difficulties, did not publish from about 1941 until the immediate post-war period. Zander wrote in his obituary on the scientist: “Heavy personal burdens, the air attacks on Berlin, besides clinical responsibilities in the Gynaecological Hospital of the Charité, no longer allowed scientific publications” [Zander 1981, p. 83].
Questions of patent law that arise from this fact cannot be considered here. It may be appropriate here to say no more than that the European steroid producers in those years had entered into various agreements not to block each others’ patents. Tausk speaks in this connection of the “Hormone cartel”153.

Undoubtedly of great importance for the relatively slow reception of ethinylestradiol was the discovery of the estrogenic effect of the stilbenes. These preparations could – as mentioned – be made easily and cheaply. They were likewise orally highly active and in the initial phase of the clinical testing (because of their wide therapeutic range) they were easier to use than the estrone derivative. They were therefore able to attract the attention of a considerably wider range of clinicians. The innumerable investigations of these compounds, carried out at the end of the 1930s and in the 1940s, provide evidence of this. But they also show, that even at that time there was a lively interest in a cheap estrogen, with good oral activity, although hormonal contraception was still far away. The first indication for use was the climacteric syndrome.

The Endometrium Synthesis Dose was Determined much Later

In the early American papers on clinical trials of ethinylestradiol, the originally used high daily doses (in the milligram range) were soon abandoned. Already from 1942 onward (Groper et al.) the hormone doses used ranged from 150 to 50 µg per day, and such doses were later also used for the first generation of contraceptives. Unfortunately, nowhere is it possible to find any indication as to what considerations or investigations were determinants for this. Thus it can only be guessed that the maximal tolerable doses were approached, so to speak, from above.

From the present standpoint this appears surprising, since with the Kaufmann experiment there already existed a model that made possible the determination of a threshold dose of a new estrogen by means of morphological findings. The investigators in the USA, however, initially restricted themselves, as Clauberg had earlier done, to fundamental detection of an estrogenic effect and testing of the compatibility of the substance. In addition to clinical observations and endometrium findings, in the many studies of the treatment of the postmenopausal syndrome, use was also made of vaginal cytology. First indications of the endometrium synthesis dose came after 1944 in papers by W. Allen, Bickers and Birnberg. Its more accurate determination remained reserved – so far as can be seen to German authors at the beginning of the 1950s. At that time, ethinylestradiol had already been introduced into therapy.

It is now known, that with ethinylestradiol at 50 µg per day a plateau in the proliferation of the endometrium is attained. The dose of 5 µg is adequate to restore an atrophied vaginal epithelium to its premenopausal condition. In a group of climacteric women, 80% could be freed of hot flushes with a dose of 15 µg per day, but an increase of this dose brought no further improvement in the result. Ovulation can certainly be stopped only with 100 µg, a circumstance that because of the clearly increased morbidity risk at this dose, leads to a contraceptive based only on ethinylestradiol appearing contraindicated154.

The position that ethinylestradiol at the present time still occupies, as the most used estrogen component of hormonal contraceptives, more than 70 years after its discovery, has already been indicated in the introduction. It has also already been mentioned, that ethinyltestosterone must be considered as forerunner of a large group of artificial progestins, that at the present time are indispensable for treatments with sex hormones. Both are here in conclusion once again called to mind, in order to underline the importance of the work that chemists, physiologists and clinicians have done in connection with the discovery of both substances.

Conflict of Interest

The research for this article was supported by a grant from the former Schering AG Berlin.

153 See in addition [Tausk M. Organon. The story of an unusual pharmaceutical enterprise. Published by Akzo Pharma bv, Oss, The Netherlands 1984; 88–93.]
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