Retro-steroids
A new class of compounds with sex-hormone action

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Introduction

The interdependence of the various organs, tissues and cells of an organism requires the presence of a communication system by means of which the different parts can act upon one another. If a rapid reaction is required the human body generally makes use of the nervous system, while for less rapid but longer-lasting effects the hormone system comes into play. Both systems are very closely co-ordinated.

The hormones, which bring about their effects via the bloodstream, are produced in glands with internal secretion, or endocrine glands. The sex hormones are produced in the pituitary gland, in the ovaries of the female, and in the testes of the male. The pituitary gland is a tiny gland lying at the base of the brain and closely connected with the nervous system. In man and woman it produces identical hormones, which have a stimulating action on the production centres in the sex glands and are therefore called "gonadotropic hormones" (gonad = sexual gland, tropic = directed towards). The hormones produced in the ovaries and in the testes are different; the most important ones are the estrogens and progesterone in the ovaries and testosterone in the testes. In addition to their specific sex-hormone action in male and female, these affect in their turn the production of gonadotropic hormones. Control of the production of hormones is thus obtained by means of feedback.

The gonadotropic hormones and the hormones produced in the sex glands belong to two different classes of chemical compounds, the polypeptides (proteins) and the steroids respectively.

The steroid group of sex hormones began to receive considerable attention in about 1930 from many research workers, both in scientific and industrial laboratories. This was not because the steroid hormones are medically more important than the others, but because it has been found possible to produce steroid hormones and variants of them synthetically. Control of the production of hormones is thus obtained by means of feedback.

The steroid group of sex hormones began to receive considerable attention in about 1930 from many research workers, both in scientific and industrial laboratories. This was not because the steroid hormones are medically more important than the others, but because it has been found possible to produce steroid hormones and variants of them synthetically. This is not yet possible for the gonadotropic hormones.

Steroids are abundantly represented in living organisms, both animal and vegetable, and they are also interesting because, although structurally closely related, they exhibit widely different physiological action. Digitalis, a drug which is prepared from the foxglove, has an action on the human heart and has been used since 1785 in the treatment of heart disorders. Cholesterol is found in the blood and in all tissues of the animal organism; it plays an important part in the building up of cell membranes. Bile acids play a part in the digestion of fats. Provitamin D is converted by ultra-violet irradiation into vitamin D, which prevents rickets. Finally, the steroids also include the cortical adrenal hormones, which fulfil such an essential function in the body that the removal of the adrenal gland results in death within a few days.

In about 1930, at the time when the chemical structure of the sex hormones was established, intensive investigations were started with the object of synthesizing naturally-occurring steroids. Later on, efforts were made, by introducing all kinds of structural variations, to prepare substances possessing a more powerful or better, i.e. more selective, action than the natural hormones. These efforts succeeded remarkably well. Steroid research received a fresh stimulus in 1949, when cortisone, an adrenal cortical hormone, was found to alleviate rheumatoid arthritis. The latest powerful incentive to further research on steroids was the discovery of the contraceptive action of some steroids: the invention of "the pill", about ten years ago.

The interest of Philips-Duphar in steroids is as old as this company itself. As long ago as 1938 an article appeared in this journal describing how Philips embarked upon vitamin D research as a result of efforts to find applications for ultra-violet lamps[1].

Chemistry of the steroids

The steroids are defined chemically as a class of organic compounds with a polycyclic structure, consisting of four linked carbon rings: three rings of six carbon atoms and one of five. The carbon skeleton, with the conventional numbering of the carbon atoms and with the letters denoting the rings, is given in fig. 1a; fig. 1b gives a spatial representation of the carbon skeleton.

Fig. 2 shows the structural formulae of several steroid compounds which are mentioned in this article, in particular the female sex hormones estradiol and progesterone, the male sex hormone testosterone, and ergosterol (a compound related to cholesterol).

The work of analysing these structures has been long and laborious; for an account of this the reader is referred to the literature [21]. We shall only mention here that treatment of different compounds with selenium led to the formation of one and the same product, methylcyclopentenophenanthrene:

This proved clearly and elegantly that the above compounds were indeed related.

The main function of the selenium is that it removes hydrogen from the six-membered-carbon rings of the steroid skeleton, so that these become unsaturated. This aromatization, as it is called, is accompanied by the removal of fragments from the carbon skeleton such as the methyl groups 18 and 19. The living organism is also capable of aromatization, but in this case it generally remains limited to ring A. We shall return later in more detail to this physiologically extremely important reaction in the living organism.

The saturated steroid skeleton contains various asymmetric carbon atoms, that is to say, carbon atoms which are linked by their four valency bonds to four different atoms or groups of atoms. Two spatial arrangements are possible for an asymmetric carbon atom, and each is the mirror image of the other.

As can be seen in fig. 2 testosterone and progesterone have six asymmetric carbon atoms; estradiol has one less and ergosterol has as many as eight. The presence of \( n \) asymmetric carbon atoms means that it is possible to have \( 2^n \) compounds with the same chemical structure but with different spatial configuration (stereoisomers). We have already mentioned that steroid compounds, with their close structural relationship, show considerable differences in physiological properties. Their physiological action is extremely sensitive to changes in chemical structure, and this may also be expected to apply for changes in their spatial structure. It has been found, however, that in nature, in both vegetable and animal organisms, mainly one stereochemical structure is used for the widely different tasks which the steroid compounds have to fulfil. Indeed, this preference for one particular spatial configuration is the rule rather than the exception in nature. It is a well-known fact, for example, that the amino acids, from which proteins are built up, occur exclusively with an L-configuration, and never with its mirror image, the D-configuration.

As indicated by the heading, this article is concerned with retro-steroids. These are steroids in which the natural spatial configuration has been artificially changed at the two carbon atoms 9 and 10 to that of the mirror image.

**Chemistry of the retro-steroids**

The retro-structure can be obtained by ultra-violet irradiation of "provitamin D", which consists of ster-
oids having two unsaturated bonds between carbon atoms 5 and 6 and between 7 and 8. A great deal of work has been done in this field at the Central Laboratory of Philips-Duphar, at Weesp, Netherlands [3], in co-operation with research workers of the Laboratory for Organic Chemistry, Leyden University [4]. The decision to start synthesis of retro-steroids was taken in 1956 by Reerink, under whose supervision the irradiation research at Weesp took place. By this time it was already possible to give some indications of the chemical reactions occurring during irradiation. These are shown in fig. 3.

As can be seen in the diagram, irradiation has the effect of breaking the bond between the carbon atoms 9 and 10. This bond can be reconstituted by further irradiation under the right conditions. In principle the mirror-image configurations at carbon atoms 9 and 10 can occur when this ring is formed again.

The different configurations are denoted by the letters α and β. In this notation the steroids are characterized by a 9α,10β-configuration; and the retro-steroids by a 9β,10α-configuration.

The starting material used in the investigations at Weesp was ergosterol (see fig. 2), a compound which is related to cholesterol and is easy to isolate from vegetable sources. The retro-form of this compound — at first just a by-product of the production of vitamin D$_2$ — was to play a leading part in the research at Weesp under the name of lumisterol$_2$.

![Fig. 3. Diagram showing the reactions that take place when a provitamin D is irradiated. R is an alkyl group.](image)

![Fig. 4. Reaction diagram for the preparation of retro-progesterone and retro-testosterone from lumisterol$_2$.](image)

The diagram of fig. 4 shows the manner in which the retro-configurations of the sex hormones testosterone and progesterone can be synthesized from lumisterol$_2$. As well as this we have prepared many other compounds with interesting biological activity [5]. Three of these are selected for further discussion:

1) the 6-dehydro-retro-progesterone, or dydrogesterone, which is now marketed under the name of "Duphaston" [4];
2) the 16α-ethylether of dydrogesterone;
3) the 17α-(2'-methallyl)-retro-testosterone.

The preparation of these compounds is indicated in the diagram of fig. 5. A special method was used for the second compound. Not all carbon atoms of the steroids are equally accessible for chemical substitution, and indeed for the last ten years or so derivatives have been made with the aid of micro-organisms, which sometimes have a highly specific hydroxylating action. Research in this direction indicated that micro-
organisms can also convert retro-steroids. A case in point was the successful use made of the mould Sepedonium ampullosporum for the conversion of dydrogesterone into its 16a-hydroxy derivative, which was further converted into the corresponding 16a-ethylether by means of the usual chemical methods.

To conclude this section we show in fig. 6 the marked change that occurs in the spatial structure as a result of conversion into the retro-form.

**Pharmacological action**

Work on synthetic substitutes of the sex hormones generally has the following aims in view:

a) to reinforce or weaken certain effects of natural hormone activity, with the aim of increasing its specificity;

b) to obtain activity after oral administration — most natural sex hormones are inactive after oral administration.

In what follows we shall show some of the results we have been able to achieve with retro-steroids, taking the three compounds mentioned as examples. First, however, it is necessary to know a few elementary facts about the menstrual cycle in women and about the changes that take place at the beginning of pregnancy.

After puberty there is regular menstrual bleeding. This is caused by the shedding of the inner lining of the womb, the endometrium, which has been subjected to the action of the estrogens and progesterone.

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tion) and the cells in which the ovum was embedded develop into a gland with internal secretion, the corpus luteum, which, in addition to estrogens, now produces progesterone. The progesterone is thus produced only in the second half of the cycle, while the estrogens are active during the whole of the cycle (fig. 7). Since progesterone is formed and starts to work only after the ovum has been discharged from the ovary, it is easy to understand that the principal task of this hormone is to ensure that the ovum, if it is fertilized, will be able to become implanted in the inner lining of the womb, which has been prepared for this by the progesterone (fig. 7 and fig. 8). If no fertilization takes place, the corpus luteum degenerates. The production of hormone ceases, and as a result of this the whole endometrium is shed; this manifests itself as menstrual bleeding. A renewed ripening of a Graafian follicle then starts and the process starts all over again. The whole process takes about 28 days.

The production of estrogens and also of progesterone during the cycle is stimulated by the hormones which are produced in the pituitary gland. Putting it very simply, we may say that the gonadotropic hormone FSH (follicle-stimulating hormone) stimulates the production of estrogen as well as the growth of the Graafian follicle, while the inducing of ovulation (bursting of the follicle) and the production of progesterone are stimulated by the gonadotropic hormone LH (luteinizing hormone). This is shown in the cyclic menstrual diagram of fig. 7. The cyclic behaviour results because estrogens and progesterone can in turn inhibit the production of FSH and LH.

If fertilization of the ovum does take place, a hormonal stimulus (HCG, see the pregnancy diagram in fig. 9) goes to the ovary from the fertilized ovum implanted in the endometrium. This ensures that the corpus luteum does not degenerate and that the production of progesterone is therefore maintained.

Fig. 7. Interaction of the gonadotropic hormones FSH and LH from the pituitary gland and the estrogens (E) and progesterone (P) from the ovary, and their effects on the ovary and the endometrium (the inner lining of the womb) during a normal menstrual cycle.

Fig. 8. Further details of the changes taking place in the endometrium during the menstrual cycle. The first phase in the build-up, called the proliferative phase, is controlled by the estrogens. Glands, blood vessels and other cell tissues are formed. In the second, or secretory phase, which is controlled by progesterone, the blood-vessels and glands take on a rather more convoluted appearance, and the glands also begin to secrete substances capable of nourishing a fertilized ovum. At the climax of this phase the endometrium is about 7 mm thick. In the pre-menstrual phase the growth of the endometrium diminishes due to the reduced supply of blood, the termination of the glandular secretions and loss of water.
Furthermore, the fertilized ovum itself starts to make progressively more and more progesterone. As a result the endometrium is preserved and no menstruation occurs during pregnancy. The production of gonadotrophic hormones in the pituitary is inhibited during pregnancy, so that there is no renewed ripening of follicles and therefore no further ovulation. All this can be considered as a protection for the embryo: if there were any further ovulations, the released ova could also be fertilized and would endanger the originally fertilized ovum.

Fig. 9. Diagram showing the implantation of a fertilized ovum in the endometrium, and the accompanying changes in hormone concentration. The diagram shows a continuation of the production of estrogens and progesterone compared with the production in a normal menstrual cycle (fig. 7). From about the 25th day of the cycle a hormonal stimulus HCG goes out from the fertilized ovum. The dashed part of the curve HCG was obtained by extrapolation.

A second action which progesterone has is directly connected with this protective function. During ovulation the cervix uteri (the external orifice of the womb) is subjected to the influence of the estrogens alone. These make certain that the glands, present here in great abundance, give off a thin secretion which greatly facilitates the penetration of spermatozoa, so that fertilization is able to take place. The progesterone, which is produced after ovulation and is also present in high concentration during pregnancy, exerts a marked thickening action on the cervical mucus so that the passage of spermatozoa is made very difficult or even impossible. Here again, the protective action of which we have mentioned. The developing embryo in the womb is extremely sensitive to all kinds of hormonal action, and therefore any substitute for progesterone must not possess any hormonal side-effects. It is not sufficient for a synthetic product to show progestational action in appropriate tests; it must also be thoroughly investigated to see if the substance has any undesirable side-effects on the foetus.

In the early stages of the search for progestational compounds that would be active after oral administration, work was largely concentrated on male hormone substances which have certain activities in common with progesterone. When this progestational action was in-
tensified by bringing about certain changes in structure.
the male action did not as a rule completely disappear.
In experiments on animals \( ^8 \) the drawback of
administering such substances during pregnancy was
therefore particularly apparent with female embryos.
These types of compound could not therefore be con-
sidered for use in maintaining a human pregnancy.

At the time when we started work on retro-pro-
gesterone there were very few, if any, progestational
substances for oral administration that did not have
one or more hormonal side-effects. When it had been
found that oral administration of retro-progesterone
gave progestational action and that 6-dehydro-retro-
progesterone or dydrogesterone gave even greater
action, these compounds were subjected to the appro-
priate experiments, in which all kinds of progestational
action could be determined as well as other possible
hormonal side-effects. Dydrogesterone was found to
have no action not found in natural progesterone \( ^9 \).

It does not however have all the actions of the
natural hormone. For example, this retro-steroid does
not have the thermogenetic effect of the natural
hormone. If the-temperature of an adult non-pregnant
woman is recorded daily (before she gets up in the
morning) it is found that in the second half of her cycle,
i.e. after ovulation has taken place, her temperature is
0.5 °C to 1 °C higher than in the first half of her cycle.
The body temperature is also slightly higher during
pregnancy than it was in the period preceding the ovu-
lation that led to fertilization. This makes it possible to
find out, by taking the temperature of a patient being
treated with dydrogesterone, whether the body has
started to produce its own progesterone. The break-
down of this retro-steroid in the body also takes a dif-
f erent course from that of the natural hormone (see
last section), so that the excretion products of the
body's own progesterone can be determined in addition
to those of dydrogesterone. This has distinct advan-
tages for diagnosis and therapy. During treatment with
dydrogesterone it is thus possible to find out whether
the body's own production during pregnancy, for ex-
ample, has become high enough after a certain period of
time (since the implanted ovum is also going to make
progesterone itself) for treatment with the pregnancy-
maintaining drug to be stopped or adapted. We are in
fact able to say that dydrogesterone is a substance with
distinct advantages for use as a substitute for progester-
one \( ^{10} \). These advantages are:

a) its great similarity to the natural hormone progester-
one, as proved in progestational tests;
b) its oral activity;
c) the total absence of hormonal side-effects (no vir-
ilizing effect);
d) It does not interfere with diagnosis.

One other property in which dydrogesterone differs
from progesterone has not yet been mentioned. As we
have said, the action of progesterone prevents ovulation
from occurring after pregnancy has begun. Dydro-
gesterone does not have this ovulation-inhibiting action
of progesterone. Even in very large doses the substance
has no inhibiting effect on the mechanism causing
ovulation in the normal cycle \( ^{10} \).

Because of this combination of properties, dydroges-
terone in certain cases shows not only a pregnancy-
maintaining effect, but can also promote pregnancy.
Where infertility is due to the body's insufficient pro-
duction of progesterone, for example, treatment with
dydrogesterone can bring the endometrium to an op-
timum state without reducing the chance of ovulation,
thus increasing the chances of pregnancy.

The 16α-ethylether of dydrogesterone

We shall now deal with a second substance which
has a progestational action, but which is specialized to a
very much greater extent in its activity. This substance,
16α-ethylether of dydrogesterone, exhibits only very
slight progestational action on the endometrium and
like dydrogesterone, it does not inhibit ovulation. The
only indication of its progestational action is the marked
thickening of the cervical mucus that occurs after
administration. This thickened mucus acts, as we have
seen, as a barrier to sperm cells.

If this substance is administered in the first half of
the cycle, i.e. before ovulation, the cervical mucus be-
comes very viscous. Normally at this time the cervical
mucus is only subject to the effects of estrogens and is
a rather thin fluid. Although at this time the cervical
mucus should promote fertilization by allowing the
rapid and unobstructed passage of sperm cells, their
passage is hampered as a result of the administration
of this substance (and hence also of other progestatio-
nally active compounds). The substance might there-
fore act as an impediment to pregnancy, without
bringing about other progestational effects. This
brings us to the interesting question of whether this
action could be taken as the basis of a contraceptive
preparation.

Presumably, the principal action on which most
such preparations depend is the one which inhibits the
gonadotropic substances from the pituitary gland. The
underlying mechanism is based on an imitation of the
processes during pregnancy which prevent the occur-
rence of ovulation. Nevertheless, there are indications
that a number of women using such contraceptive
measures do still have ovulations, with no resulting
pregnancy. This absence of pregnancy is probably due
to other (local) effects of the contraceptive preparation,
i.e. on the oviducts, the womb and the cervical mucus,
reducing the probability of fertilization or hindering the process of implantation.

In all probability, the proportion of estrogens to progesterone in the various preparations has an important bearing on their different kinds of action, but it would take us too far afield to go into this subject here.

The search for substances with a contraceptive action is still in progress, with particular emphasis on these local effects. The action which has been found for 16a-ethyl ether of dydrogesterone is in this connection highly significant.

17a-(2'-methallyl)-retro-testosterone

Not every cycle is accompanied by an ovulation. In such cases the endometrium is therefore not affected by the progesterone. This may sometimes give rise to menstrual irregularities, resulting in fairly prolonged bleeding.

We have not yet touched on the fact that the action of progesterone must in general be preceded by the action of the estrogens. In a few cases high doses of progesterone itself can bring about an effect, but the addition of a small amount of estrogen increases the action of progesterone considerably (synergistic action).

If enough endometrium activated by estrogen is still present the progestational substance is generally able to stop excessive bleeding like that mentioned above, since progestational changes can still be brought about in the endometrium. The treatment artificially reproduces the pattern of an ovulatory cycle. If treatment with the progestational agent is then stopped, normal menstruation will usually follow.

In cases of very persistent bleeding, in which progestational agents do not help, we can still stop the bleeding by giving an anti-estrogenic substance.

The substance 17a-(2'-methallyl)-retro-testosterone is such a substance. Experiments specially designed to assess estrogenic action showed this substance to be active as an antagonist of estrogen. The substance was found to be able to antagonize both the body's own estrogens and those administered artificially, e.g. by injection. Persistent bleeding occurring after a non-ovulatory cycle is stopped by this substance within 48 hours.

To be assured of safe application of a retro-steroid as a pharmaceutical it is necessary to have a detailed knowledge of any changes it may undergo in the body. This is the subject of the next section.

Conversions of the retro-steroids in the body

In all the interactions of hormone regulation taking place in the body, it is obviously important that the steroid hormones should be inactivated and excreted after performing their function. This inactivation takes place mainly in the liver: here the body has a series of enzyme systems at its command which attack the steroid molecules.

The first inactivating reactions consist of reductions of the 3-keto group and the double bond between C4 and C5. First, the double bond between C4 and C5 is reduced, which causes a new centre of asymmetry to appear at C5. There are individual enzymes which give rise either to the 5α or the 5β compounds (5α and 5β reductases). Reduction of the 3-keto group then follows. This is the normal way in which saturated 3α-hydroxy-steroids are produced in the body. Apart from these initial reactions, various other conversions take place. If a keto group is present at C20, it is reduced; in a number of 17-OH compounds the whole side chain is split off, and sometimes hydroxyl groups are introduced at various places. The saturated compounds are coupled to glucuronic acid or sulphuric acid and this imparts a polar character to the whole compound which enables it to be rapidly excreted via the urine.

In accordance with the above, the urine of pregnant women is found to contain pregnane-3a,20a-diolglucuronide as the principal metabolite of progesterone (fig. 10).

![Fig. 10. Conversion of progesterone into a product which is excreted in the urine.](image)

It appeared interesting to investigate the behaviour of the retro-steroids towards the enzymes that attack the natural steroids.

First of all, the behaviour of the 5α and 5β reductases, obtained from the liver of rats, was investigated. These occur at different places in the liver cells and can be obtained separately. The naturally-occurring steroids are quickly reduced by these enzymes. Synthetic derivatives from these natural steroids may sometimes be attacked with a little more difficulty; thus, for example a double bond between C6 and C7 is found to make...
the reaction considerably slower. The behaviour of the above enzymes towards retro-steroids of widely varying kinds can be summed up quite simply: none of the retro-steroids is reduced. This also applies in particular to the substances mentioned above, dydrogesterone, the 16α-ethylether of dydrogesterone and 17α-(2'-methallyl)-retro-testosterone. The chief initial attack which the normal steroids are subjected to in the body is apparently unable to take place with the retro-steroids.

As previously mentioned, the 20-keto group in progesterone is also reduced. The relevant enzyme, the 20-keto reductase, was now also investigated to obtain some knowledge of its behaviour towards retro-progesterone and dydrogesterone. In contrast to what was found with the 5-reductases, 20-keto reductase was in fact able to reduce the above retro-steroids. With the enzyme from the rat the reduction was found to proceed at the same rate as with progesterone; with an enzyme preparation of human origin the reduction of the retro-compounds proceeded rather more slowly than that of progesterone.

The enzyme that reduces the 20-keto group attacks a group located in the side chain of ring D of the steroid molecule, a location at quite a considerable distance from those locations that give the retro-configuration its specific character. Perhaps this explains why the 20-keto reductase does attack the retro-steroids while, as we have seen, the 5-reductase does not.

The above results, which were obtained with isolated enzymes in vitro, are in complete agreement with what is known up to now about the breakdown of retro-steroids in the body. If radioactively labelled dydrogesterone is taken by women, the principal metabolite appearing in the urine is found to be the glucuronide of the compound which has been reduced at the C20 site (fig. 11). In contrast to what happens with progesterone, we find no reduction of the A-ring here, but only a reduction of the keto group at C20. There is thus quite a difference, compared with the metabolism of progesterone.

The reactions which dydrogesterone undergoes are thus more limited than those of, say, progesterone, but in fact these reactions proceed so rapidly that if dydrogesterone is given to women orally, about 40% of the dose is excreted in the urine within eight hours.

Apart from the above reactions which lead to inactivation and rapid excretion, we are naturally also concerned with the many reactions in the body by which hormones are synthesized and converted one into the other. Let us consider for example the estrogenic steroids, which are characterized by an aromatic A-ring. Living tissues form these substances by aromatization reactions from testosterone and androsterone, for instance as shown by the diagram in fig. 12.

![Fig. 11. Conversion of dydrogesterone into an excretion product.](image1)

![Fig. 12. Simplified diagram of the synthesis in the body of the female sex hormone estradiol.](image2)
These estrogens can also be made _in vitro_ by using certain systems of enzymes occurring in the "microsome fractions" of the cells of various organs and allowing these enzymes to react with, for example, testosterone. An enzymatic system from human placenta, which has this property, was also investigated to see if it would aromatize steroids having the retro-structure. Here it was found that the retro-steroids in question were not attacked by the particular enzyme system [13]. Aromatization of retro-testosterone, for example, could not be demonstrated, while on the other hand these steroids also exhibited no trace of estrogenic action in animal experiments after reaction with the enzyme. These experiments give an indication that when these steroids are administered to humans there will be no estrogenic side-reactions due to aromatization. This absence of estrogenic side-effects is again in agreement with what is known about the biological properties of dydrogesterone [14].

Owing to the dissimilar configuration of the retro-steroids it may of course happen that the molecules do not "fit" so well at the receptor sites of those organs through which the compounds are active. But once molecules are obtained with a sufficiently good "fit" to give biological activity, and dydrogesterone serves here as an example, we then have gained the advantage that the compound is less easily converted by the body into related steroids. As we have seen in the example of dydrogesterone the reactions which give rise to excretion products take place sufficiently quickly, but they are limited in number when compared with the natural steroids and their derivatives. With the retro-steroids there is therefore little fear of side-effects due to conversion into other hormonally-active steroids, so that in general an action exclusively in accordance with the purpose of the treatment is to be ensured.

Summary. The sex hormones which are produced by the ovaries and testes: estrogens, progesterone and testosterone etc., belong to the steroids. Retro-steroids are steroids with a 9\(\beta\),10\(\alpha\) configuration, which can be obtained by the irradiation of provitamin D. The pharmacological properties and metabolism of three of these compounds, which differ from normal steroid hormones in their spatial structure, are examined here. Dydrogesterone ("Duphaston") can be taken orally as a substitute for progesterone, for example where there is a risk of miscarriage. It serves not only to maintain but also to promote pregnancy. The 16\(\alpha\)-ethylether of dydrogesterone is characterized by a specific action on the cervical mucus. The compound 17\(\alpha\)-(2'-methallyl)-retro-testosterone is characterized by an anti-estrogenic action which may explain why it can be used to stop persistent non-ovulatory menstrual bleeding. The conversions of the retro-steroids in the body take place differently from those of natural steroids. There is for example no aromatization of the A-ring, and therefore little fear of conversion into other hormonally-active steroids which could lead to side effects.

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In the Cyclotron and Isotope Laboratories

The Cyclotron and Isotope Laboratories have recently been set up by N.V. Philips-Duphar in the grounds of the Netherlands Reactor Centre at Petten. The chemical processing of the radioactive material produced in the laboratories is carried out in cabinets termed "hot cells". The maintenance gangway shown gives access to the back of these hot cells. When maintenance or repair work is required the lead shields of the hot cells can be moved aside or removed. This is of course only done after removing as much of the radioactive material as possible from the hot cell. Access to the gangway is restricted to specially trained and equipped personnel, under the supervision of the laboratory medical department. The man working on the right is wearing an oxygen mask; the man on the left is wearing a pressure suit supplied with air by the hose lying on the floor.

The pressure in the gangway is kept below that in the hot cells to prevent radioactivity from being carried to the workroom in front of the cells by particles of dust, etc. The pipelines are for ventilating the cells.