

Zeitschrift: Bulletin der Schweizerischen Akademie der Medizinischen Wissenschaften = Bulletin de l'Académie suisse des sciences médicales = Bollettino dell' Accademia svizzera delle scienze mediche

Herausgeber: Schweizerische Akademie der Medizinischen Wissenschaften

Band: 25 (1969)

Artikel: Metabolism of progesterone and synthetic progestational agents

Autor: Breuer, H.

DOI: <https://doi.org/10.5169/seals-307771>

Nutzungsbedingungen

Die ETH-Bibliothek ist die Anbieterin der digitalisierten Zeitschriften auf E-Periodica. Sie besitzt keine Urheberrechte an den Zeitschriften und ist nicht verantwortlich für deren Inhalte. Die Rechte liegen in der Regel bei den Herausgebern beziehungsweise den externen Rechteinhabern. Das Veröffentlichen von Bildern in Print- und Online-Publikationen sowie auf Social Media-Kanälen oder Webseiten ist nur mit vorheriger Genehmigung der Rechteinhaber erlaubt. [Mehr erfahren](#)

Conditions d'utilisation

L'ETH Library est le fournisseur des revues numérisées. Elle ne détient aucun droit d'auteur sur les revues et n'est pas responsable de leur contenu. En règle générale, les droits sont détenus par les éditeurs ou les détenteurs de droits externes. La reproduction d'images dans des publications imprimées ou en ligne ainsi que sur des canaux de médias sociaux ou des sites web n'est autorisée qu'avec l'accord préalable des détenteurs des droits. [En savoir plus](#)

Terms of use

The ETH Library is the provider of the digitised journals. It does not own any copyrights to the journals and is not responsible for their content. The rights usually lie with the publishers or the external rights holders. Publishing images in print and online publications, as well as on social media channels or websites, is only permitted with the prior consent of the rights holders. [Find out more](#)

Download PDF: 08.07.2025

ETH-Bibliothek Zürich, E-Periodica, <https://www.e-periodica.ch>

B. Metabolism of Endogenous Progesterone and Synthetic Progestational Agents

Institut für Klinische Biochemie der Universität Bonn

Metabolism of Progesterone and Synthetic Progestational Agents

H. BREUER

During the last fifteen years the metabolism of progesterone has been extensively investigated in many laboratories. The present paper is concerned with some aspects of the metabolic pathways undergone by progesterone and by synthetic progestins. The discussion will be restricted as far as possible to the results pertaining to humans.

1. Progesterone

The metabolism of progesterone consists of a number of complex processes which are all potentially variable. These processes include 1. reduction, 2. hydroxylation and 3. conjugation (Fig. 1). Reduction of the progesterone molecule may occur at the C-3 oxo group, at the C-20 oxo group and in ring A, thus yielding 5 α - and 5 β -pregnane derivatives. Indeed, the main metabolite of progesterone in man is the fully reduced compound 5 β -pregnane-3 α ,20 α -diol. Hydroxylations at C-6 and C-16 give rise to 6-oxygenated and 16 α -hydroxylated metabolites which account for most of the so-called "polar fraction". Recently, HARKNESS, DAVIDSON and STRONG (1969) obtained evidence from in vivo experiments that there is appreciable hydroxylation of the progesterone molecule at positions other than C-6 and C-16. In man, the majority of metabolites of progesterone is excreted in urine principally as glucuronides, and only a small fraction is conjugated with sulphate. However, when large amounts of progesterone are metabolized, there may be an increase in the sulphate fraction (HARKNESS, DAVIDSON and STRONG, 1969).

As can be seen from Fig. 2, the reductive metabolism of progesterone leads, theoretically, to the formation of 20 metabolites. Not included in this scheme are the 6 epimeric allylic alcohols. So far, only 5 of the possible 20 metabolites have been isolated after incubation of progesterone with a "suspension" of human liver (ATHERDEN, 1959). These include 5 α - and 5 β -pregnane-3,20-dione, 3 α - and 3 β -hydroxy-5 α -pregnan-20-one, 3 α -hydroxy-5 β -pregnan-20-one and 5 β -pregnane-3 α ,20 α -diol. The amounts of metabolites

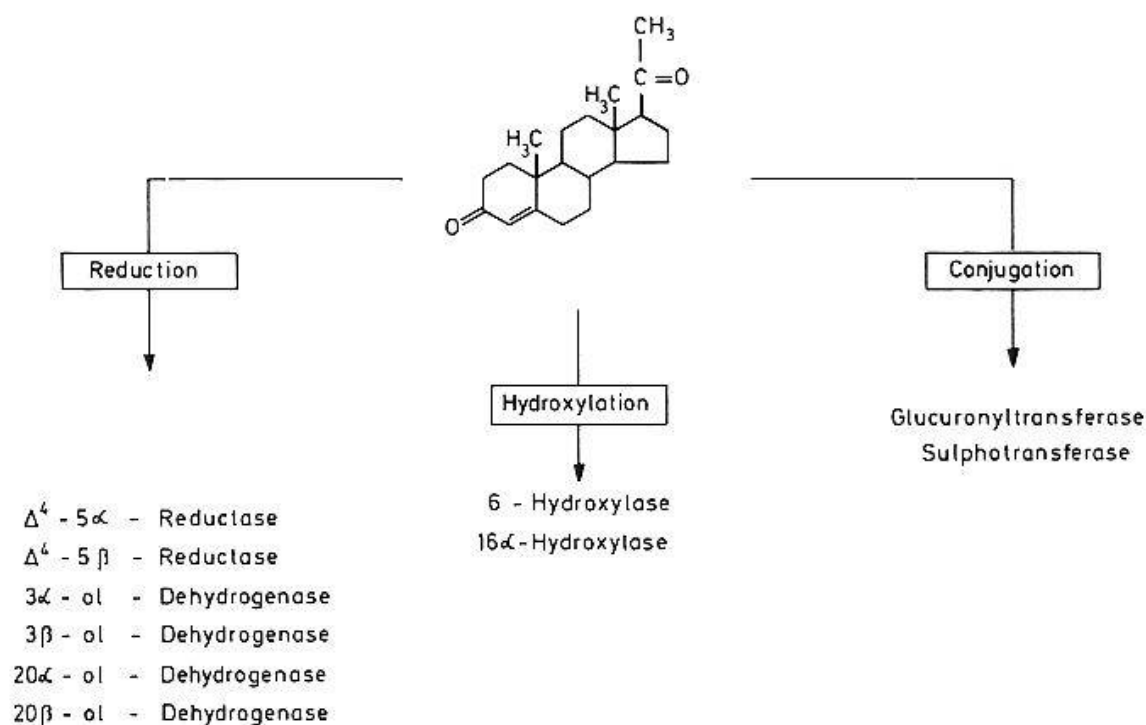


Fig. 1. Main metabolic pathways of progesterone, and enzymes involved in the reduction, hydroxylation and conjugation of progesterone and its metabolites.

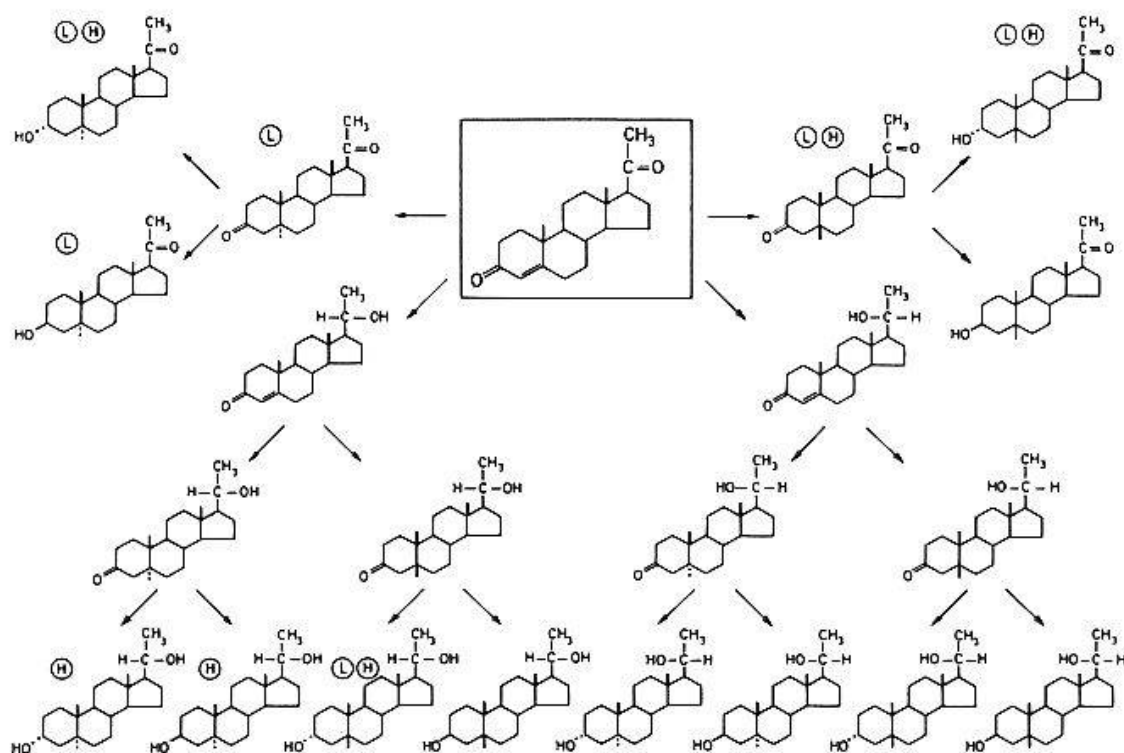


Fig. 2. Reductive metabolism of progesterone. L = Metabolite found after incubation of progesterone with a "suspension" of human liver (ATHERDEX, 1959); M = metabolite found in urine after administration of progesterone to man (for references, see LANG-ECKER, 1968).

isolated in these experiments seem to indicate that, for progesterone, the main metabolic pathway in human liver is progesterone \rightarrow pregnanediol \rightleftharpoons pregnanolone \rightleftharpoons pregnanediol (Fig. 3). It is interesting to note that the metabolism of progesterone in the rat appears to be different from that in the human. On the other hand, the identity of the metabolites obtained with rabbit liver (TAYLOR, 1955) and human liver (ATHERDEN, 1959) suggests that the rabbit may be a useful species for the study of progesterone metabolism, although the conversion of progesterone to pregnanediol involves different pathways in the rabbit and in man (COOKE, ROGERS and THOMAS, 1963).

Although progesterone is metabolized largely by the liver rather than by the biosynthetic systems in steroid producing organs, much effort has been directed towards the study of the metabolism of progesterone in the ovary. The principal reactions are demonstrated in Fig. 4. Progesterone may be reduced at the 3-oxo group without change of the Δ^4 -double bond. The 3-hydroxy derivative thus formed is progestationally active (DORFMAN, 1967). No special significance seems to be associated with hydroxylation at position C-6. The introduction of the 16 α -hydroxy group results in the formation of a compound which is biologically inactive. However, the possibility must be considered that the 16 α -hydroxy derivative may be an intermediate in the biosynthesis of estriol. The 17 α -hydroxylation of progesterone is recognised to be the initial step in the biosynthesis of androgens and estrogens. The demonstration of this reaction in ovaries has been relatively extensive. The reduction of the 20-oxo group gives rise to the 20 α -dihydro and 20 β -dihydro derivatives of progesterone, both of which have progestational activity and are therefore to be regarded as progestins (ZANDER, FORBES, v. MÜNSTERMANN and NEHER, 1958).

Numerous studies have been carried out on the metabolism of progesterone in vivo in man under a variety of experimental conditions. Although the elucidation of the metabolic pathways has been greatly facilitated by the use of the radioactive hormone, there are still many outstanding points awaiting solution. Qualitatively, most of the metabolites isolated from urine after the administration of progesterone to human subjects are identical with those formed in incubation experiments with human liver (compare Fig. 2). In addition, 6-oxygenated and 16-hydroxylated compounds were also identified (for details, see FOTHERBY, 1964). Quantitatively, the most important single metabolite of progesterone is 5 β -pregnane-3 α ,20 α -diol, excreted almost entirely as the glucuronide. Wide variations occur in the percentage conversion of progesterone to pregnanediol. Thus, using tritium-labelled progesterone, 6–27% of the administered dose was excreted as pregnanediol, 1.6–5% as pregnanolone, and 0.5–2% as pregnanediolone (PEARLMAN, 1957; CONTRACTOR and PEARLMAN, 1960). The conversion of progesterone to pregnanediol is neither influenced by pregnancy (PEARLMAN, 1957; PLOTZ, WIENER and DAVIES, 1963) nor by different phases of the menstrual cycle (for details, see FOTHERBY, 1964) nor by the removal of endocrine glands

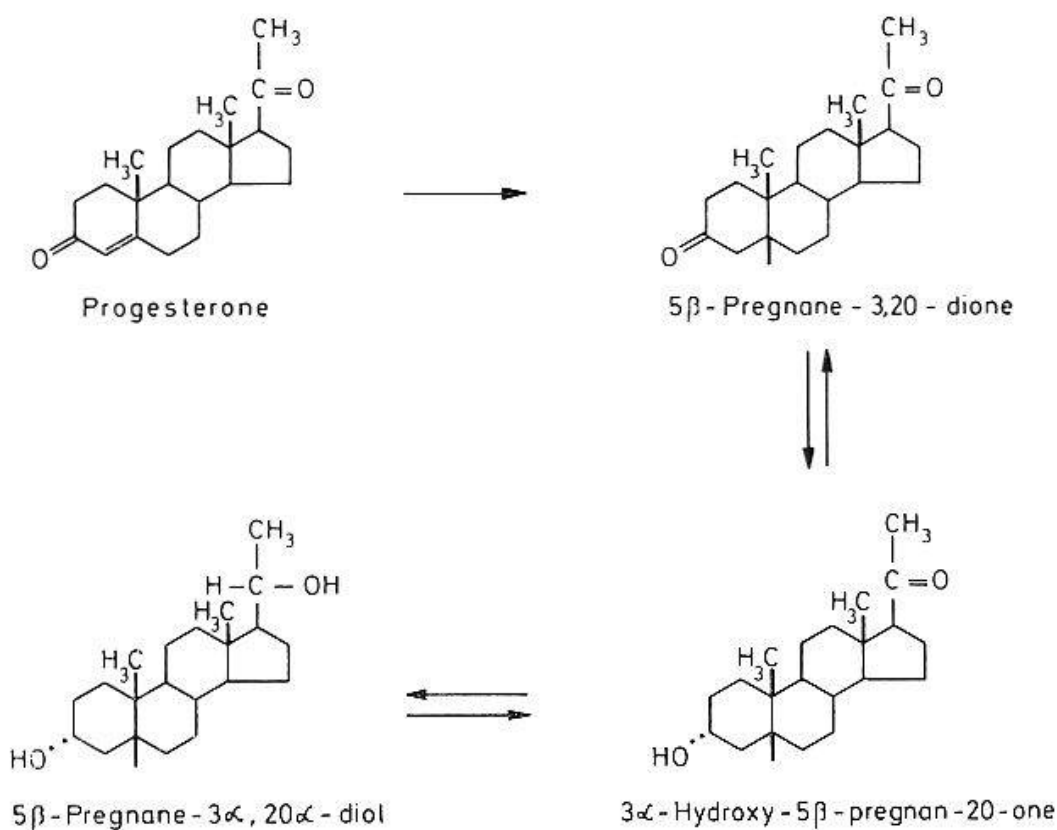


Fig. 3. Main metabolic pathways of progesterone in human liver (ATHERDEN, 1959).

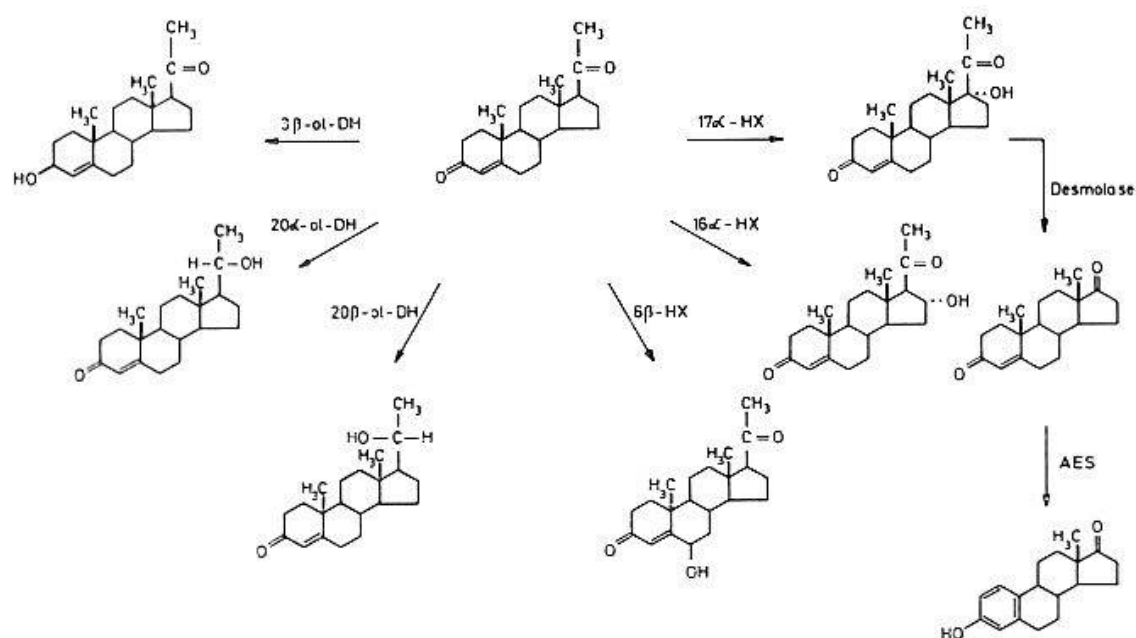


Fig. 4. Main metabolic pathways of progesterone in ovarian tissue. ol-DH = hydroxysteroid dehydrogenase, HX = hydroxylase, AES = aromatizing enzyme system.

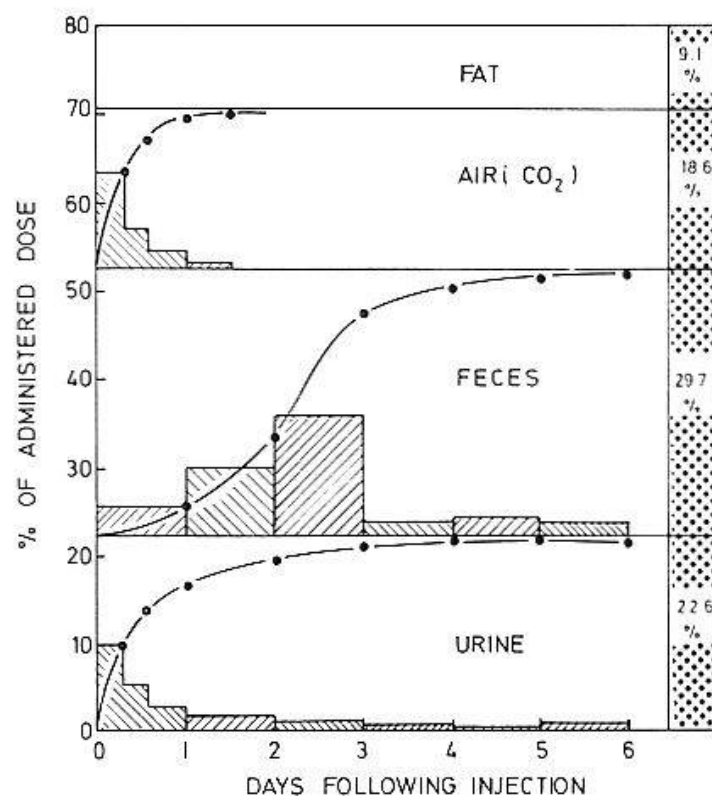


Fig. 5. Radioactivity in urine, feces, expired air and body fat following intravenous administration of $[21-^{14}\text{C}]$ progesterone to a pregnant woman. According to PLOTZ (1961).

such as ovaries and adrenals (PEARLMAN, 1957). However, relatively long term changes in thyroid function (BRADLOW, FUKUSHIMA, ZUMOFF, HELLMAN and GALLAGHER, 1966), nutritional status (HARKNESS, DAVIDSON and STRONG, 1969), or age (ROMANOFF, MORRIS, WELCH, GRACE and PINCUS, 1963) will alter the pattern of progesterone metabolism.

In a very elegant and competent manner, PLOTZ and DAVIS have studied the metabolic fate, the distribution and the excretion of the metabolites of progesterone in the human (DAVIS and PLOTZ, 1957a, b; PLOTZ and DAVIS, 1957; DAVIS and PLOTZ, 1958; PLOTZ, 1961; PLOTZ, 1962). Following the intravenous injection of $[21-^{14}\text{C}]$ progesterone, a total of 22.6% and 29.7% was excreted in the urine and feces, respectively (Fig. 5). Approximately 18–19% was excreted by way of the lungs within 30 h. After this time, no radioactivity could be discovered in the expired carbon dioxide. Fig. 6 shows the excretion pattern and the total amounts of radioactivity in urine and feces of a pregnant patient, following a single intramuscular application of $[4-^{14}\text{C}]$ progesterone. The fact that no radioactivity could be detected in the expired air makes it likely that ring A of the steroid molecule is not split into such small fragments as carbon dioxide during its metabolism. On the basis of these investigations, PLOTZ (1961) suggested a diagram which illustrates the fate of progesterone in the human organism (Fig. 7). Progesterone synthesized in the endocrine glands and released into the blood disappears rapidly from the circulation due to 1. a speedy conjugation and

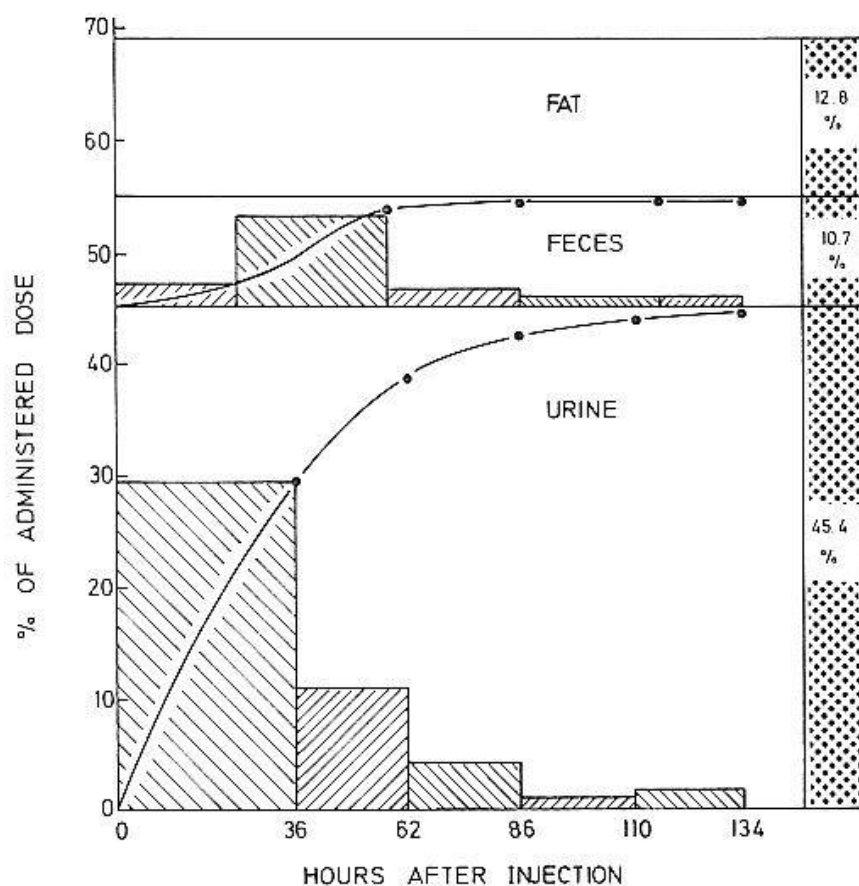


Fig. 6. Radioactivity in urine, feces and body fat following intramuscular administration of $[4-^{14}\text{C}]$ progesterone to a pregnant woman. According to Plotz (1961).

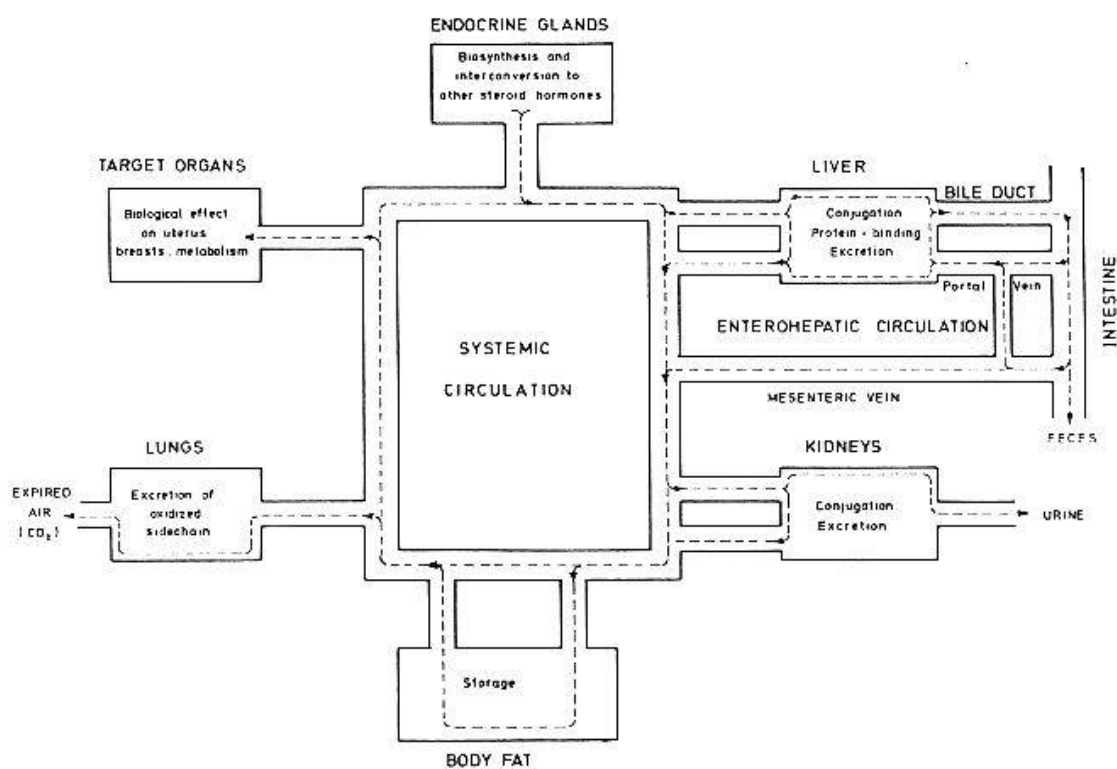


Fig. 7. Diagram illustrating the fate of progesterone in the human organism. According to Plotz (1961).

inactivation in the liver and kidneys, and 2. a rapid diffusion into body tissues, mainly into the fat compartment. The principal excretory pathways of the conjugated metabolites of the hormone are via the urine (15–61%) and the feces (13–38%) (for references, see DROSDOWSKY, DESSYPRIS, MCNIVEN, DORFMAN and GUAL, 1965). A substantial part of the metabolites excreted in the bile is reabsorbed from the gastrointestinal tract. The elimination of the C-17,21 side chain as carbon dioxide through the lungs seems to take place fairly rapidly, whereas the amount of progesterone metabolites eliminated through the skin is negligible as compared with that excreted by the other routes.

2. Synthetic progestational agents

At present, only limited information is available regarding the metabolic fate of synthetic progestins (RICHTER, 1965). So far, metabolic studies have been confined to derivatives of 19-nortestosterone, to C-6 and C-17 substituted derivatives of progesterone and to derivatives of retro-progesterone (9 β ,10 α -pregn-4-ene-3,20-dione).

The results obtained with ethynyl-19-nortestosterone (17 α -ethynyl-17 β -hydroxy-19-nor-androst-4-en-3-one) can be summarised as follows: 1. The ethynyl side chain is not reduced metabolically to the vinyl or ethyl side chain. 2. No removal of the ethynyl side chain and subsequent formation of 17-oxosteroids could be demonstrated after administration of ethynyl-19-nortestosterone to human subjects. 3. Ring A reduction of ethynyl-19-nortestosterone follows the same metabolic pathways as those of 19-nortestosterone and testosterone (BREUER, 1964). In addition to these reactions, hydroxylation at C-atom 10 plays an important role in the metabolism of progestationally active 19-norsteroids (LAYNE, GOLAB, ARAI and PINCUS, 1963).

It has been suggested that the remarkably enhanced hormonal activity of progesterone, when substituted at C-6 and C-17 in the steroid nucleus, is due to increased resistance to metabolizing enzymes (GLENN, RICHARDSON and BOWMAN, 1959; BUSH, 1962). In fact, it was found that one of these substituted progesterones, megestrol acetate (17 α -acetoxy-6-methyl-4,6-pregnadiene-3,20-dione) is very resistant to metabolism in vitro by liver preparations from rats and rabbits as compared with progesterone (COOKE and VALLANCE, 1965). It is probable that the 6 α -methyl and 17 α -acetoxy groups block metabolism by inhibiting reduction of the Δ^4 -3-oxo and C-20-oxo groups, respectively (Fig. 8). Introduction of a Δ^6 -bond, in addition to the 6-methyl and 17 α -acetoxy groups, into the progesterone molecule, as in megestrol acetate, gives further protection to metabolising enzymes, possibly by inhibiting hydroxylation at the C-6 position.

In 1960, REERINK, SCHÖLER, WESTERHOF, QUERIDO, KASSENBAAR, DICZFALUSY and TILLINGER announced a new class of hormonally active steroids, named "retro-steroids" (Fig. 9). This class is characterized by the β -position of the C-9 hydrogen atom and the α -position of the C-10 methyl group. Two

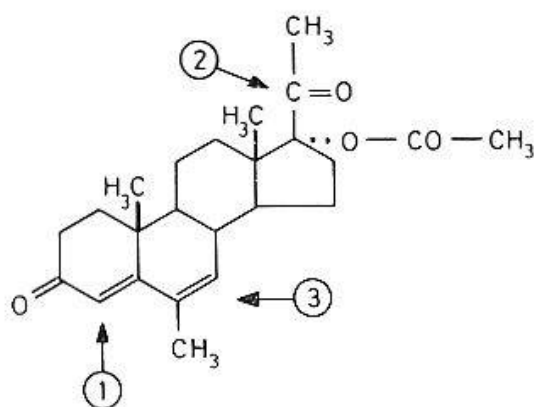
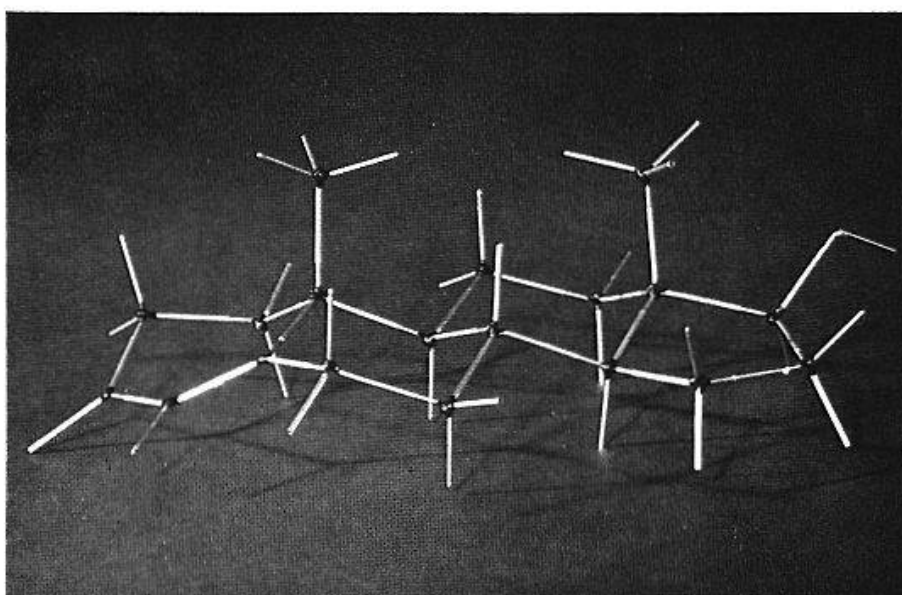


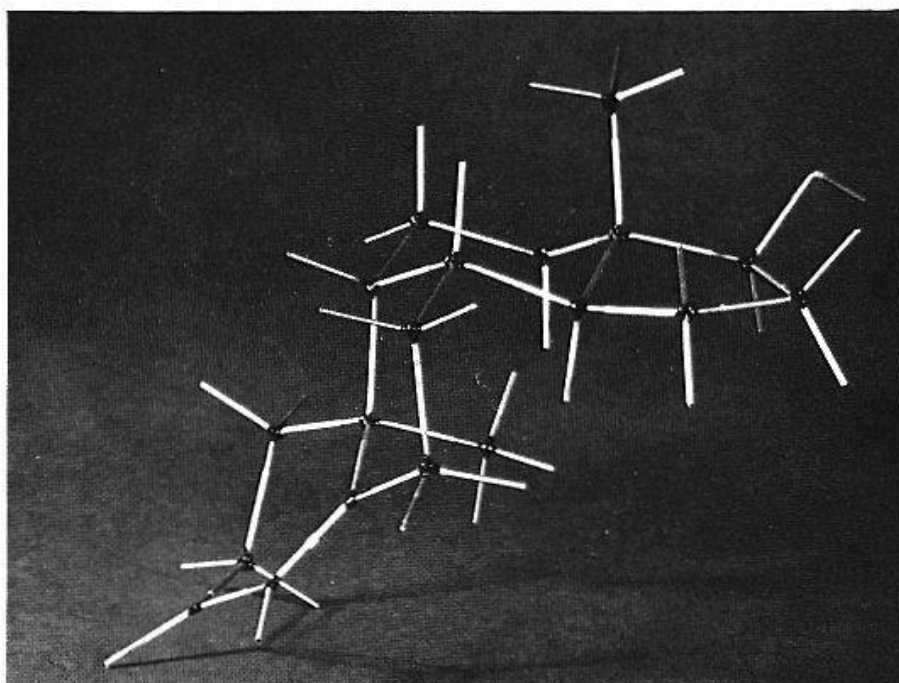
Fig. 8. Positions of megestrol acetate which are resistant to metabolism by liver preparations (COOKE and VALLANCE, 1965). (1) = Δ^4 -3-oxo group, (2) = C-20-oxo group, (3) = C-atom 6 (no hydroxylation).

members of this class, 6-dehydro-retroprogesterone ($9\beta,10\alpha$ -pregna-4,6-diene-3,20-dione) and retroprogesterone ($9\beta,10\alpha$ -pregn-4-ene-3,20-dione) were found to exert a markedly progestational activity when administered orally. This suggested the possibility that their metabolism would be different from that of progesterone (Fig. 10). After oral administration of 6-dehydro-retroprogesterone to postmenopausal women, the main metabolite detected in urine was 20 α -hydroxy- $9\beta,10\alpha$ -pregna-4,6-dien-3-one, whereas retroprogesterone yielded 20 α -hydroxy- $9\beta,10\alpha$ -pregn-4-en-3-one (DICZFALUSY, TILLINGER, ESSER and HOUTMAN, 1963). No 20 α -hydroxypregn-4-en-3-one is excreted in urine after administration of progesterone, whereas the principal urinary metabolites of the two retrosteroids investigated are the 20 α -hydroxylated forms. Therefore, the results obtained by DICZFALUSY and his colleagues indicated major differences in the metabolism of progesterone and retroprogesterone.

More recently, a new potent progestationally active retrosteroid, Ro 4-8347 (6-chloro- $9\beta,10\alpha$ -pregna-1,4,6-triene-3,20-dione) has been studied in clinical trials. In view of the possible significance of this compound, its metabolism was investigated in vitro with human and rat liver preparations, and in vivo in man and rats. In previous studies (BREUER and KNUPPEN, 1969) it had been shown that, in contrast to the naturally occurring C_{19} -retrosteroids the Δ^4 -3-oxo group in C_{19} -retrosteroids is not reduced by the Δ^4 -5 α - and Δ^4 -5 β -reductases. Similarly, during incubation of retroprogesterone with human liver preparations, no decrease of the absorption at 240 m μ was observed (Fig. 11); under the same conditions, the Δ^4 -3-oxo group of progesterone is rapidly reduced. As was to be expected, no reduction of the Δ^4 -3-oxo group took place when Ro 4-8347 was incubated with slices of human or rat liver. Further experiments were carried out to obtain more information about the metabolic fate of Ro 4-8347. It was found that, during incubation with liver slices of male rats, the substrate was rapidly transformed to a "polar" metabolite A (Fig. 12); in contrast, liver slices of female rats metabolized Ro 4-8347 much slower, and only traces of a "polar"



a



b

Fig. 9. The spatial structure of a) the normal steroid skeleton (Δ^4 -3-oxo steroid),
b) the retrosteroid skeleton (Δ^4 -3-oxo 9β , 10α -steroid).

metabolite could be detected after 80 min of incubation (Fig. 12). This remarkable sex difference was observed in 6 male and 6 female rats. To identify the "polar" metabolite A, a large-scale experiment with liver brei of male rats was performed. After paper and thinlayer chromatography in various systems, metabolite A was obtained in crystalline form. Its physical and chemical properties as well as its behaviour towards microchemical reactions are summarized in Table I. These data already suggested that metabolite A might be identical with the 16α -hydroxy derivative of

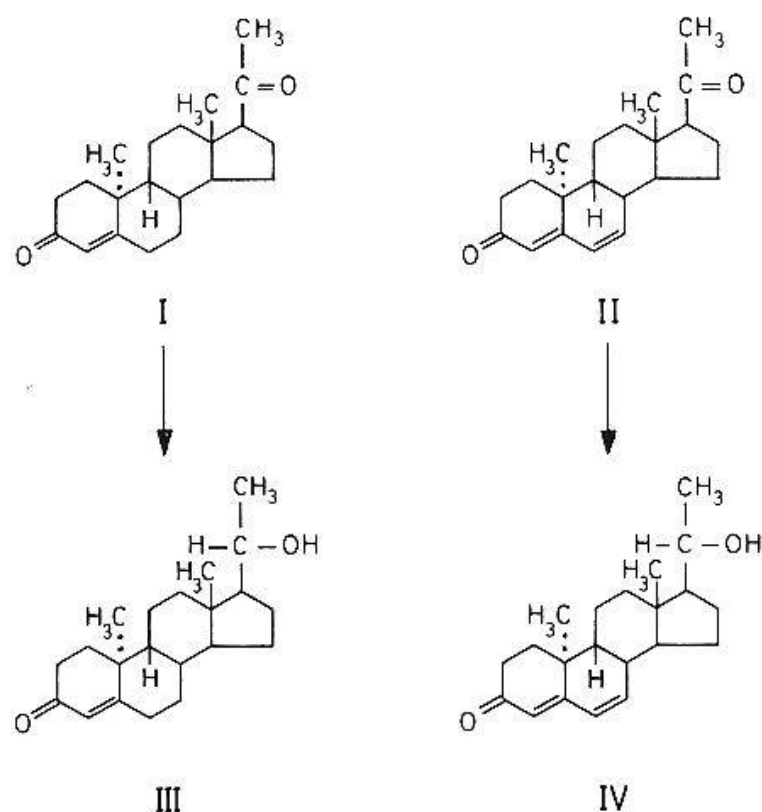


Fig. 10. Metabolism of retroprogesterone (I) and 6-dehydro-retroprogesterone in post-menopausal women (DICZFALUSY, TILLINGER, ESSER and HOUTMAN, 1963). The 20 α -alcohols III and IV were isolated from urine after oral administration of I and II, respectively.

Table I

Physical and chemical properties, and microchemical reactions of metabolite A, formed during incubation of Ro 4-8347 with liver slices of male rats

Melting point	159-160° C
Infrared spectrum	Bathochromic shift for 20 carbonyl group
Ultraviolet spectrum	Maxima at 227, 254 and 301 m μ
Treatment with:	
Sodium bismuthate	No reaction
Acetic anhydride	Formation of a monoacetate
Chromic acid	No reaction

Ro 4-8347. Definite proof of the identity of metabolite A with 6-chloro-16 α -hydroxy-9 β ,10 α -pregna-1,4,6-triene-3,20-dione was obtained after comparison with the authentic compound. It should be noted that, in addition to the 16 α -hydroxy compound, no other metabolites were found in the experiments with rat liver slices.

In view of the well-known species differences in the metabolism of progesterone, it seemed of interest to study the biotransformation of Ro 4-8347 also in human liver slices. It was found that, independent of sex and age,

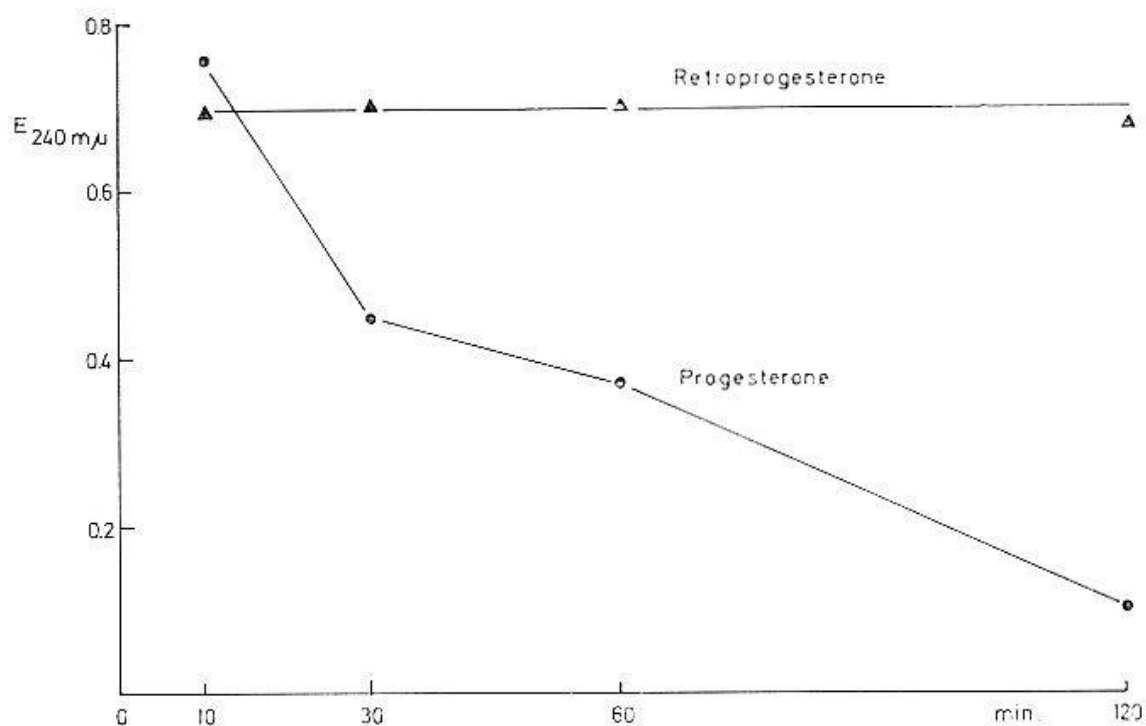


Fig. 11. Changes of the ultraviolet absorption at 240 $m\mu$ during incubation of retroprogesterone and progesterone with human liver slices. 100 μg of each steroid was incubated with 200 mg of human liver slices in Krebs phosphate buffer, pH 7.4, at 37° C for 120 min. The incubation media were extracted with ether/chloroform; after evaporation the residues were dissolved in ethanol and portions of the ethanolic solutions taken for measuring the ultraviolet absorption.

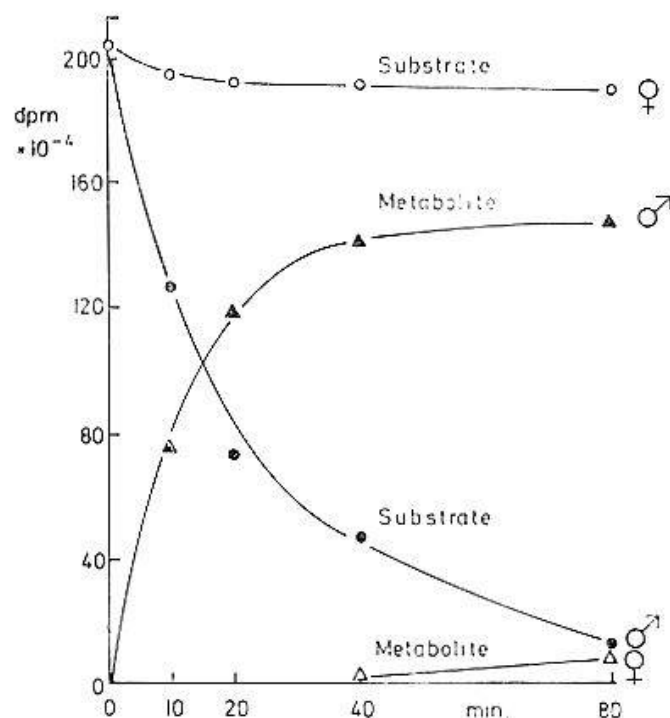


Fig. 12. Metabolic transformation of Ro 4-8347 by liver slices of male and female rats. Each point of the curves represents the mean values of 6 male and 6 female rats. 100 μg [3H] Ro 4-8347 was incubated with 100 mg of liver slices of male or female rats in Krebs phosphate buffer, pH 7.4, at 37° C. The incubation media were extracted with ether/chloroform; after evaporation, the residues were chromatographed on formamide-impregnated paper with cyclohexane/benzene (3:2). The chromatograms were scanned in a Packard radiochromatogram scanner model 7200.

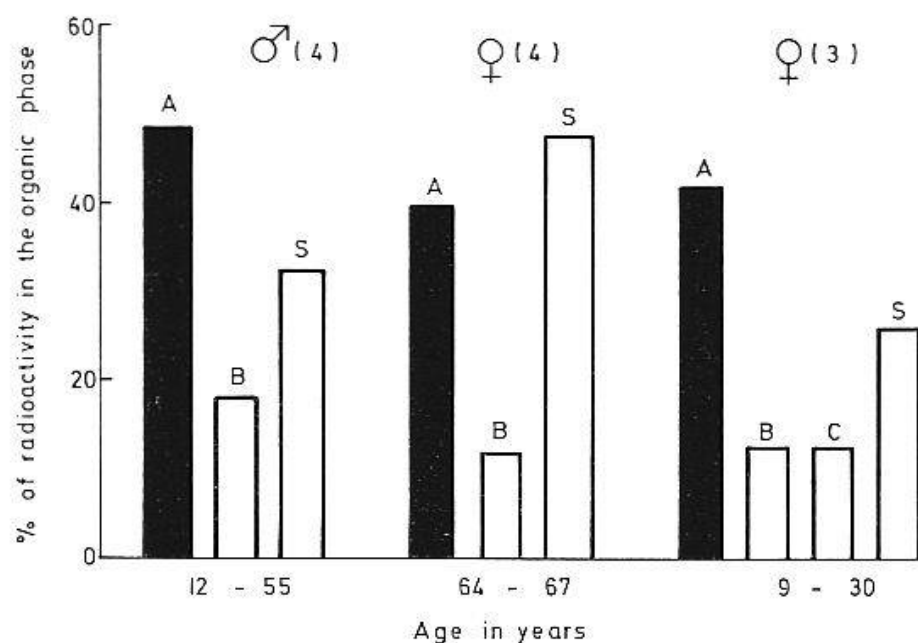


Fig. 13. Metabolic transformation of Ro 4-8347 by human liver slices. 100 μ g [7- 3 H] Ro 4-8347 was incubated with 100 mg of human liver slices in Krebs phosphate buffer, pH 7.4, at 37° C; for further details, see legend to Fig. 12. The columns represent mean values, the number of patients is given in brackets. - A = metabolite A, B = metabolite B, C = metabolite C, S = Ro 8347.

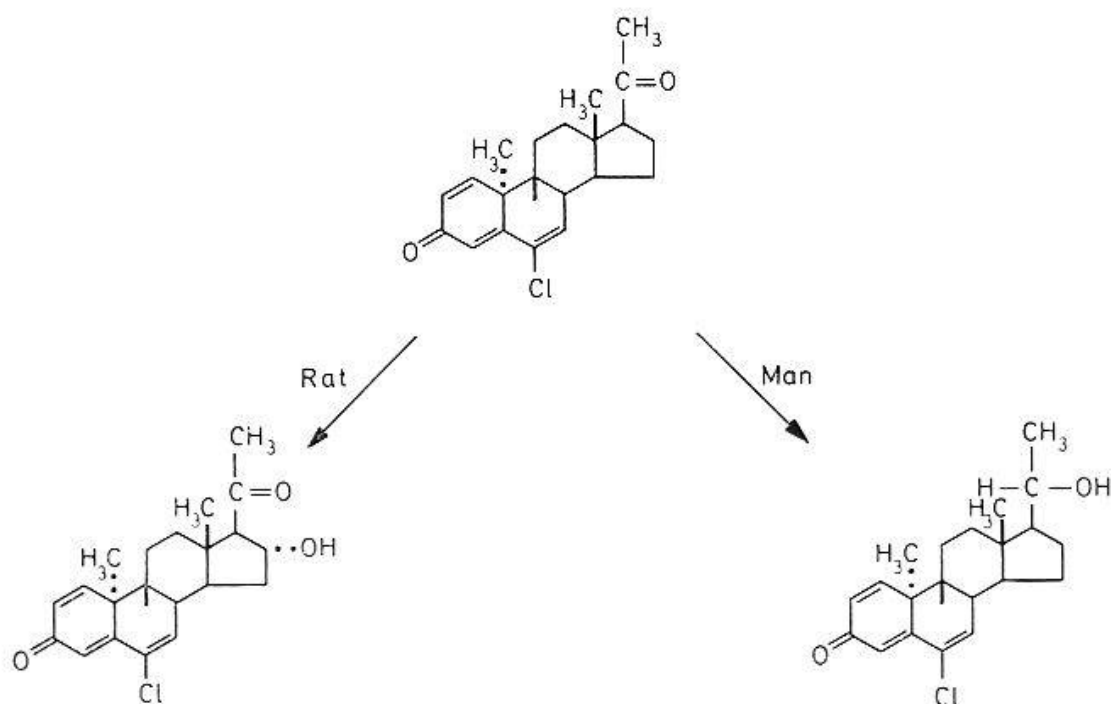


Fig. 14. Main metabolites formed during incubation of Ro 4-8347 with liver slices of man and of male rats. For details of identification, see text.

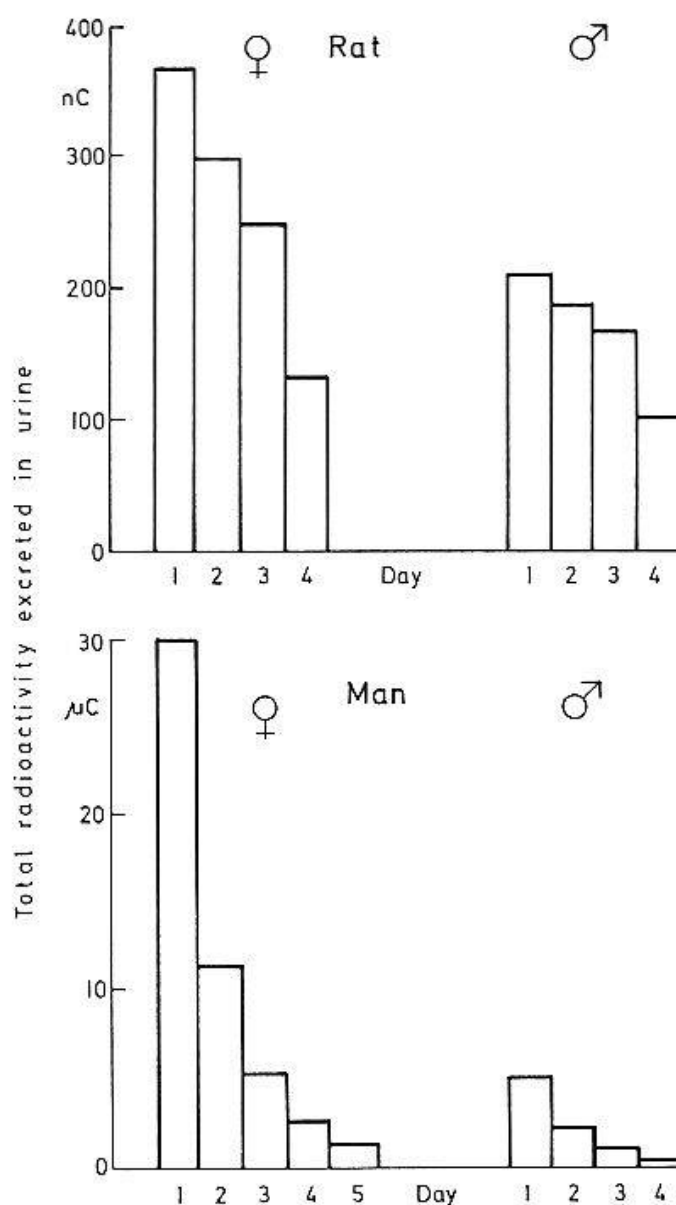


Fig. 15. Total radioactivity excreted in urine after oral administration of [7-³H] Ro 4-8347 to human subjects and to rats (2 female and 2 male rats). The radioactivity administered was 101 μ Ci in the experiments with human subjects, and 10 μ Ci in the experiments with rats.

the steroid was more rapidly metabolized by human liver than by rat liver. In all experiments, two metabolites (A and B) were detected, one of which (metabolite A) was formed in larger amounts (Fig. 13). A third metabolite (C) was only found when it was incubated with liver tissue from two younger women and one girl. To identify the main metabolite, formed in human liver, the following experiments were carried out. Crystallization from ethyl acetate yielded a substance which melted at 155–159° C. The ultraviolet spectrum revealed the presence of the three characteristic maxima for the $\Delta^{1,4,6}$ -3-oxo group. From the infrared spectrum, it was concluded that the metabolite still contained a 3-oxo group, whereas the 20-oxo group of the substrate had disappeared. Using paper chromatography, the identity of

the metabolite with the 20 β -hydroxy derivative could be excluded. Finally, by comparison with the authentic steroid, the main metabolite proved to be identical with 6-chloro-20 α -hydroxy-9 β ,10 α -pregna-1,4,6-triene-3,20-dione.

The main metabolites formed during incubation of Ro 4-8347 with liver slices of man and of male rats are shown in Fig. 14. Further experiments are necessary to identify metabolites B and C, of which, so far, metabolite C has been detected only in liver of young females.

In preliminary experiments, the *in vivo* metabolism of Ro 4-8347 was studied in human subjects and in rats. After oral administration of the steroid, the main metabolite isolated from human urine was the 20 α -hydroxy compound, whereas the 16 α -hydroxy compound was the main metabolite in rat urine. These results agree with those obtained under *in vitro* conditions with liver tissue. Of particular interest are the results of the excretion studies. The amount of total radioactivity, excreted in urine after a single dose of tritiated Ro 4-8347, was considerably greater in a human female than in a human male (Fig. 15). Thus, in the female, about 50% of the administered dose was excreted in urine within 5 days, whereas in the male less than 10% was excreted. A similar, although less prominent sex difference was found in rats; again female rats excreted more of the administered radioactivity in urine than did the male rats.

Conclusion

The results reported here demonstrate that, in man and rat, the metabolism of Ro 4-8347 is quite different from that of progesterone. Furthermore, species differences exist. In man, the 20-oxo group is reduced to the 20 α -hydroxy group, whereas in rat the steroid is hydroxylated in position 16 α . Finally, preliminary excretion studies revealed interesting sex differences which require further investigation.

- ATHERDEN L. M.: Progesterone metabolism: Investigations of the products of metabolism with human liver *in vitro*. *Biochem. J.* **71**, 411-415 (1959).
- BRADLOW H. L., FUKUSHIMA D. K., ZUMOFF B., HELLMAN L. and GALLAGHER T. F.: Influence of thyroid hormone on progesterone transformation in man. *J. clin. Endocr.* **26**, 831-834 (1966).
- BREUER H.: Studies on the metabolism of 17 α -ethinyl-19-nortestosterone. *Int. J. Fertil.* **9**, 181-187 (1964).
- BREUER H. and KNUPPEN R.: Stoffwechsel von 9 β ,10 α -Testosteron in Gewebepräparationen der Rattenleber und der Nebenniere des Rindes. *Hoppe-Seylers Z. physiol. Chem.* **350**, 581-590 (1969).
- BUSH I. E.: Chemical and biological factors in the activity of adrenocortical steroids. *Pharmacol. Rev.* **14**, 317-445 (1962).
- CONTRACTOR S. F. and PEARLMAN W. H.: [16-³H]Progesterone metabolism in advanced pregnancy and in oophorectomized-hysterectomized women: urinary ketonic metabolites. *Biochem. J.* **76**, 36-41 (1960).
- COOKE A. M., ROGERS A. W. and THOMAS G. H.: The urinary metabolites of progesterone labelled with tritium and carbon-14 in the rabbit. *J. Endocr.* **27**, 299-315 (1963).
- COOKE B. A. and VALLANCE D. K.: Metabolism of megestrol acetate and related progesterone analogues by liver preparations *in vitro*. *Biochem. J.* **97**, 672-677 (1965).

- DAVIS M. E. and PLOTZ E. J.: The metabolism of progesterone and its clinical use in pregnancy. *Recent Progr. Hormone Res.* **13**, 347-379 (1957a).
- DAVIS M. E. and PLOTZ E. J.: Progesterone, the pregnancy hormone. *Fertil. a. Steril.* **8**, 603-618 (1957b).
- DAVIS M. E. and PLOTZ E. J.: Hormones in human reproduction II. Further investigation of steroid metabolism in human pregnancy. *Amer. J. Obstet. Gynec.* **76**, 939-953 (1958).
- DICZFALUSY E., TILLINGER K. C., ESSER R. J. E. and HOUTMAN A. C.: Metabolism of some progestationally active $9\beta,10\alpha$ -steroids in man. *Nature (Lond.)* **200**, 79-80 (1963).
- DORFMAN R. I.: The metabolism of progesterone in the ovary. *Europ. Rev. Endocr. Suppl.* **2**, part 2, 209-221 (1967).
- DROSDOWSKY M. A., DESSYPERIS A., MCNIVEN N. L., DORFMAN R. I. and GUAL C.: A search for progesterone in human urine. *Acta endocr. (Kbh.)* **49**, 553-557 (1965).
- FOTHERBY K.: The biochemistry of progesterone. *Vitam. a. Horm.* **22**, 153-204 (1964).
- GLENN E. M., RICHARDSON S. L. and BOWMAN B. J.: Biologic activity of 6-alpha-methyl compounds corresponding to progesterone, 17-alpha-hydroxyprogesterone acetate and compound S. *Metabolism* **8**, 265-285 (1959).
- HARKNESS R. A., DAVIDSON D. W. and STRONG J. A.: The metabolism of small and of large amounts of progesterone in man. *Acta endocr. (Kbh.)* **60**, 221-236 (1969).
- LANGHECKER H.: Resorption, Verteilung und Ausscheidung der Gestagene, in: *Handbuch der experimentellen Pharmakologie, Die Gestagene*, Part 1: p. 264-351, ed. by K. JUNKMANN. Springer, Berlin/Heidelberg/New York 1968.
- LAYNE D. S., GOLAB T., ARAI K. and PINCUS G.: The metabolic fate of orally administered ^3H -norethynodrel and ^3H -norethindrone in humans. *Biochem. Pharmacol.* **12**, 905-911 (1963).
- PEARLMAN W. H.: [^{16-3}H]Progesterone metabolism in advanced pregnancy and in oophorectomized-hysterectomized women. *Biochem. J.* **67**, 1-5 (1957).
- PLOTZ E. J.: Studies with labelled progesterone in human pregnancy. *Brook Lodge Symposium on Progesterone*, p. 91-102. The Upjohn Co., Michigan 1961.
- PLOTZ E. J.: Metabolism of progestins. *Acta cytol. (Philad.)* **6**, 213-215 (1962).
- PLOTZ E. J. and DAVIS M. E.: The distribution of radioactivity in human maternal and fetal tissues following the administration of C^{14} -4-progesterone. *Proc. Soc. exp. Biol. (N.Y.)* **95**, 92-96 (1957).
- PLOTZ E. J., WIENER M. and DAVIS M. E.: Effect of administered progesterone on urinary excretion of endogenous pregnanediol in pregnancy. *Amer. J. Obstet. Gynec.* **87**, 1-7 (1963).
- REERINK E. H., SCHÖLER H. F. L., WESTERHOF P., QUERIDO A., KASSENBAAR A. A. H., DICZFALUSY E. and TILLINGER K. C.: A new class of hormonally active steroids. *Nature (Lond.)* **186**, 168-169 (1960).
- RICHTER R. H. H.: Neuere Perspektiven für die Kontrolle der Fertilität. *Ther. Umsch.* **22**, 542-583 (1965).
- ROMANOFF L. P., MORRIS C. W., WELCH P., GRACE M. P. and PINCUS G.: Metabolism of progesterone-4- C^{14} in young and elderly men. *J. clin. Endocr.* **23**, 286-292 (1963).
- TAYLOR W.: The metabolism of progesterone by animal tissue in vitro. 2. Factors influencing the metabolism of progesterone by rabbit liver and the investigation of the products of metabolism. *Biochem. J.* **60**, 380-388 (1955).
- ZANDER J., FORBES T. R., v. MÜNSTERMANN A. M. and NEHER R.: ^{14}C -3-Ketopregnene- 20α -ol and ^{14}C -3-ketopregnene- 20β -ol, two naturally occurring metabolites of progesterone. Isolation, identification, biologic activity and concentration in human tissue. *J. clin. Endocr.* **18**, 337-353 (1958).

Author's address: Prof. Dr. H. Breuer, Institut für Klinische Biochemie der Rheinischen Friedrich-Wilhelm Universität, D-53 Bonn-Venusberg (Deutschland).

Discussion

J. HAMMERSTEIN: Have you any idea about the other metabolites you found in the urine? You showed three bars.

H. BREUER: As far as the second metabolite, the minor metabolite, is concerned, we cannot give any definite information at the moment but this metabolite is more "polar" than the 20 α -hydroxy compound. I have no idea what the chemical nature of the compound could be. Only part of the administered radioactivity is excreted in the urine. Most of the radioactivity remains in the aqueous phase. So it may well be that in addition to the metabolites so far identified further metabolites are excreted in the urine which are either water-soluble or non-hydrolyzed conjugates.

P. BERMOND: I have been very much interested by your ascertainment that the nutritional status could have an influence on the transformation of progesterone to pregnanediol. Could you tell me which kind of nutritional status is supposed to have more specially an influence on or to impair this transformation? Is this a protein deficiency or a vitamin deficiency or glucose trouble or any other nutritional impairment?

H. BREUER: I cannot say this. I got this reference from a paper by HARKNESS and STRONG in 1969 (*Acta endocr. [Kbh.]* 60, 221-236 [1969]). They stated quite clearly that there is a significant effect of the nutritional status on the conversion of progesterone to pregnanediol. I suppose that more details will be published in the near future.

P. BERMOND: Prof. GRANGOT in France emphasized that rats submitted to a deprived vitamin E diet had a complete inhibition of the transformation of pregnenolone to progesterone. Would you have an idea of the exact place where this deficiency can act chemically?

H. BREUER: Well, this is a very interesting observation. I would think that it is quite possible that a vitamin deficiency may have an effect on the oxidation of Δ^5 -pregnenolone to progesterone, but I could not make any additional statement. I do not know which organ he investigated, or was it the total conversion in the animal in vivo?

P. BERMOND: In vivo.

H. BREUER: I would think that it is quite probable but I have no explanation.

H. RICHTER: Dr. Breuer, can you tell us something about the biological activity of this 20 α -hydroxy metabolite compared with the original compound?

H. BREUER: No I cannot. We did not test the biological activity of this metabolite. Perhaps Dr. Krause can say more about it.

R. KRAUSE: Insofar as tested, we have found no significant differences between the two compounds.