Steroid Induction of Porphyrin Synthesis in Liver Cell Culture

II. THE EFFECTS OF HEME, URIDINE DIPHOSPHATE GLUCURONIC ACID, AND INHIBITORS OF NUCLEIC ACID AND PROTEIN SYNTHESIS ON THE INDUCTION PROCESS

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SUMMARY

1. Steroid induction of porphyrin synthesis in liver cell culture is, in its time of onset and course of development, in all respects similar to the induction process evoked by certain foreign chemicals and drugs. Steroids and foreign chemicals have additive-inducing effects when added to cultures in suboptimal amounts; however, when added in individually optimal amounts, the intensity of induction is not enhanced nor is its latent period shortened. These results suggest that natural steroids and porphyria-inducing drugs act at the same intracellular site or sites.

2. Actinomycin D, mitomycin C, puromycin, acetyloxychloheximide, and other agents which inhibit nucleic acid and protein synthesis block the porphyrin-inducing effect of natural steroids. These results are consistent with the view that steroids, like porphyria-inducing drugs, stimulate porphyrinogenesis by inducing the formation de novo of δ-aminolevulinic acid synthetase, the rate-limiting enzyme in heme biosynthesis.

3. Certain metalloporphyrins, including iron-protoporphyrin or eme, inhibit the steroid-induction process. The ability of heme to block steroid induction supports the idea that heme and natural steroids may compete for a binding site on a hypothetical repressor protein which ultimately regulates the activity of the structural gene which codes for δ-aminolevulinic acid synthetase.

4. Uridine diphosphate glucuronic acid also blocks porphyrin induction by steroids. The blocking effect of UDP-glucuronic acid is considered to reflect the enhanced conversion of free steroid inducers to the glucuronidated or inactive derivatives. It is postulated that the ability of large amounts of glucose to inhibit the porphyrin process in vivo reflects, in part or in whole, conversion of this sugar to UDP-glucuronic acid, resulting in enhanced glucuronidation and inactivation of inducing substances.

5. The clinical implications of this steroid action on the liver are discussed, and a working hypothesis on the mechanism of steroid control of porphyrin and heme synthesis is proposed. It is considered likely that endogenously derived inducing steroids are the physiological agents which account for the periodic, spontaneous, i.e. not drug related, exacerbations of hepatic porphyria in certain patients carrying the genetic lesion of this disease.

A number of 50-II steroid metabolites derived from the transformation in vivo of hormones physiologic to man strongly induce porphyrin synthesis in chick embryo liver cells growing in primary culture (1). The structural basis for this steroid action and its possible relevance to the physiological control of heme production have been described in the preceding paper (2). It has been shown in other studies that porphyria-inducing drugs and chemicals act in the liver of animals or in tissue culture by stimulating the formation de novo of δ-aminolevulinic acid synthetase, the rate-limiting enzyme in this synthetic pathway (3, 4). This paper presents evidence that the mechanism of porphyrin induction by steroids is probably identical with that of induction by foreign chemicals and drugs. In addition, the possible relation of this novel biological activity of natural steroids to the pathogenesis of hepatic porphyria in man is discussed.

EXPERIMENTAL PROCEDURE AND RESULTS

The liver cell culture technique used in this study has been described previously (4). Essentially, chick embryo liver cells are grown for 1 day on cover slips in vials, after which the medium is changed and test chemicals are added. After an additional 20 to 24 hours, the cover slips, now overgrown with a monolayer of hepatic cell colonies, are examined for porphyrin fluorescence with a fluorescence microscope. Inducing chemicals cause the development of a red fluorescence due to accumulated excess porphyrins in cells. The intensity of fluorescence (0 to +4) is related semiquantitatively to the porphyrins that may be extracted from the cell cultures (2, 4).

Unless otherwise indicated, the effects of the various inhibitors described in the following sections were studied in cultures in which porphyrin formation was maximally induced by appropriate concentrations (approximately 5 μg per ml) of the strong steroid inducer pregnanolone (5β-pregnan-3α-ol, 20-one).
Effect of Combined Additions of Foreign Chemical and Steroid Inducers to Liver Cell Cultures

The time course of steroid induction of porphyrin in liver cells was similar to that characterizing induction by the chemical allylisopropylacetamide (4); i.e. there was a latent period of 6 to 8 hours before fluorescence became evident, after which porphyrin production increased rapidly, reaching a maximum in about 20 hours (2).

The combined addition of suboptimal-inducing amounts of AIA and each of several potent steroid inducers (2) was found to have clearly additive effects on the intensity of fluorescence. Additive effects of combined suboptimal amounts of different steroid inducers were also observed.

The inducing effect of active steroids was not blocked or enhanced by the combined addition of equimolar or higher concentrations of inactive steroids. The glucocorticoid cortisol (1 to 15 μg per ml) did not block or enhance the inducing action of potent compounds such as pregnandiol (2 to 5 μg per ml). If a steroid was inhibitory to cells at a high concentration (2), it would decrease the activity of an inducing steroid added simultaneously.

The inducing effect of steroids was reversible if the steroid-containing medium was replaced with fresh medium during the latent period of induction.

Induction by steroids failed to occur, as determined by fluorescence microscopy, if steroids were added to the cultures 3 to 4 days after the culture was started. Analogous effects on porphyrin induction by chemicals in tissue culture have been noted earlier (4).

The combined addition to the cultures of individually maximal-inducing amounts of the chemical inducer allylisopropylacetamide and of a steroid inducer did not enhance the rate of increase of porphyrin fluorescence nor lead to a shortening of the latent period of the induction process. The results of such an experiment are shown in Table I.

These results suggest that steroids and inducing chemicals probably act at the same cellular site, or, if at different sites, then at points preceding some rate-limiting step in porphyrin biosynthesis. This second possibility seems unlikely considering the rapidity of porphyrin formation in the presence of added AIA (4).

Effects of Inhibitors of Nucleic Acid and Protein Synthesis on Steroid Induction of Porphyrins

Actinomycin D—This antibiotic associates with guanine in the narrow groove of the DNA helix, and at low concentrations it preferentially inhibits DNA-directed synthesis of RNA (5, 6). Its inhibitory effects on steroid induction of porphyrin synthesis were distinct at concentrations of 0.01 μg/ml in the culture medium, and pronounced at concentrations of 0.025 to 0.050 μg/ml (Table II). At the lower inhibitory concentrations (0.01 to 0.025 μg/ml), the cultures retained excellent growth characteristics, and there was no evident morphological cellular damage as determined by phase microscopy. The addition of actinomycin D to the cultures 12 to 16 hours after the steroids had been added had less of an inhibitory effect on porphyrinogenesis than when actinomycin D was added simultaneously with the steroids.

Mitomycin C—This antibiotic produces cross-links between the two DNA strands of the helix; selectively inhibits RNA synthesis in susceptible organisms; leads to extensive degradation (denaturation) of DNA; and in larger amounts may also suppress cellular RNA and protein synthesis (7). The inhibitory effect of this agent on steroid induction of porphyrins was evident at concentrations of 10 μg/ml, but even at concentrations of 50 μg/ml it was not possible to suppress induction entirely. At the time of induction there was little cell replication in the liver cultures so that the inhibitory effects of mitomycin C are presumably attributable to the inability of RNA polymerase to use cross-linked helical DNA for RNA synthesis. Results of typical experiments with this antibiotic are shown in Table II.

Puromycin—This antibiotic inhibits ribosomal protein syn-

### Table I

<table>
<thead>
<tr>
<th>Time after additions made to cultures</th>
<th>AIA, 60 μg, fluorescence</th>
<th>Pregnanolone, 3.7 μg, fluorescence</th>
<th>Plus AIA fluorescence</th>
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<tbody>
<tr>
<td>hrs</td>
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</tr>
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<td>4</td>
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<td>Trace</td>
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<tr>
<td>6†</td>
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<td>8†</td>
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<tr>
<td>16</td>
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### Table II

<table>
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<th>Additions to culture medium</th>
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<tr>
<td>Control</td>
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<td>+3.0</td>
</tr>
<tr>
<td>Actinomycin D</td>
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<tr>
<td>0.050</td>
<td></td>
<td>+1.5</td>
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<td></td>
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<td>1.0</td>
<td></td>
<td>+1.5</td>
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<tr>
<td>2.0</td>
<td></td>
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<tr>
<td>5.0</td>
<td></td>
<td>+0.5</td>
</tr>
<tr>
<td>Control Puromycin</td>
<td>1.0</td>
<td>+3.0</td>
</tr>
<tr>
<td>2.0</td>
<td></td>
<td>+1.0-2.0</td>
</tr>
<tr>
<td>5.0-10.0</td>
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<td>+0.5</td>
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<td>0.001</td>
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<td>0.005</td>
<td></td>
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<td>40.0</td>
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<td>80.0</td>
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The possibility that steroids might interact (complex) directly in solution with heme was examined by studying the effects of added amounts of the inducing steroid, pregnanolone, on the heme spectrum in the Soret region. Solvents for these spectral determinations were aqueous 0.05 M phosphate buffer, pH 7.4, and propylene glycol. Heme was initially dissolved in 0.01 M KOH in a concentration of 1.5 mg per ml and 5 μl (7.5 μg) of 5-fluorouracil showed significant inhibition at concentrations of 20 μg per ml; and at 80 μg per ml or more, inhibition was essentially complete (Table II).

All of the inhibitors studied were capable of significantly blocking porphyrin induction at concentrations which produce little or no concomitant cell damage as determined by morphological characteristics (phase microscopy), although, as expected, at higher concentrations all of these inhibitors severely damaged the cultures. The effects on the induction process of a number of other agents which inhibit synthesis of nucleic acid precursors or which lead to the formation of spurious or defective nucleic acids were also studied. Results of typical experiments with these agents are shown in Table III. Azaserine inhibited steroid induction in concentrations of 200 μg per ml, and at concentrations of 500 μg per ml, inhibition was almost complete. Neither added glutamine (50 to 100 μg per ml) nor pyridoxal phosphate (50 to 100 μg per ml) was able to counteract inhibition by azaserine. 6-Diazo-5-oxo-L-norleucine inhibited induction at 20 μg per ml, but inhibition was not complete even at 100 μg per ml (Table III). Fluorodeoxyuridine did not inhibit in concentrations below 20 μg per ml, but distinct inhibition was observed at 100 μg per ml. 5-Fluorouracil showed significant inhibition at 25 to 50 μg per ml (Table III). 6-Mercaptopurine riboside did not inhibit even at concentrations as high as 50 μg per ml.

Effects of Metalloporphyrins on Steroid Induction of Porphyrins

Certain metalloporphyrins were previously shown (4) to suppress hepatic porphyrinogenesis induced by the chemical allylisopropylacetamide, and in this study several similar compounds derived from protoporphyrin were examined for possible inhibitory effects on steroid induction of porphyrins. These metalloporphyrins were tested in concentrations ranging from 1.5 to 7.5 μg per ml with the following results (Table IV). Iron-protoporphyrin (heme) was distinctly inhibitory at 1.5 μg per ml and the effect was pronounced at 4.5 mg per ml. Inhibition became progressively less effective as the induction process was allowed to proceed; and like the results with actinomycin D, heme addition after 12 to 16 hours of incubation did not greatly suppress porphyrinogenesis. Manganese- and zinc-protoporphyrin inhibited significantly at concentrations of 1.5 to 4.5 μg per ml. Nickel-protoporphyrin did not inhibit at concentrations up to 7.5 μg per ml. Magnesium-protoporphyrin or a mixture of chlorophylls A and B had no inhibitory effects in similar concentrations.

The addition of inhibitory concentrations of puromycin to the cultures 12 to 16 hours after induction by the steroid had been initiated blocked the enhancement of fluorescence beyond the amount developed to that point.

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this solution were added to the aqueous buffer or to the organic solvent. The amounts of pregnanolone which could be kept in solution in the aqueous medium did not exceed 10 to 20 μg per ml. In the aqueous medium, these concentrations of steroids with heme at 7.5 μg/3 ml had no effect on the shape or height of the colloidal heme absorption band in the Soret region. In propylene glycol, concentrations of pregnanolone in a solution up to 25 times greater than the concentration of heme had no effect on its absorption characteristics. These observations are interpreted to mean that inducing steroids probably do not directly complex with free heme intracellularly.

**Effects of Components of Glucose-Glucuronic Acid Synthetic Pathway on Steroid Induction of Porphyrins**

The pathway of glucose transformation into glucuronic acid via UDP is of special importance with regard to steroid metabolism because of the participation of uridine diphosphate glucuronic acid in conjugate formation and in detoxification mechanisms (12, 13). In a previous paper (2) we noted that glucuronides of even potent steroid inducers were inactive as compared with the free steroids. It was therefore of interest to study the effect on porphyrin induction in the liver cell cultures of key components of this pathway when added together with a steroid inducer (pregnanolone, 5 μg per ml) known to undergo conjugate formation with glucuronic acid in vivo.

The major intermediates in this pathway are shown in Table V. The active glucuronic acid donor is UDP-glucuronic acid, glucuronic acid being transferred from the nucleotide to a wide variety of acceptor substances such as steroids, drugs, bilirubin, etc., by the enzyme UDP glucuronosyltransferase (or UDP glucuronosyltransferases), which appears on present evidence to be localized largely in the endoplasmic reticulum (13).

Additions of each of the major components of the pathway were made in five concentrations ranging from 100 μg per ml to 1000 μg per ml. Uridine diphosphate N-acetylgalactosamine which has been shown to enhance the rate of glucuronidation of acceptor substances, presumably by protecting UDP-glucuronic acid from hydrolysis by mixed microsomal pyrophosphorylase action (14), was also studied in the same amounts. The results of these experiments are recorded in Table V where it is demonstrated that the addition of UDP-glucuronic acid, and only this component of the pathway, significantly inhibited steroid induction of porphyrin synthesis. To exclude the possible effects of contaminants in individual samples of UDP-glucuronic acid, three different preparations (Na+, K+, and NH₄ salts) from three different sources were further tested, and all showed significant inhibition of steroid induction of porphyrin synthesis. The inhibitory effect, which is not due to quenching of induced fluorescence, was observed at the 100 μg per ml concentration of UDP-glucuronic acid in one study, but this effect usually required between 100 and 250 μg per ml for demonstration. Presumably the large amounts required to show this effect reflect hydrolysis of added UDP-glucuronic acid by cellular enzymes, impermeability of the cell membrane to the nucleotide, etc. Attempts to increase the inhibitory action of UDP-glucuronic acid when added in small amounts (25 to 100 μg) by concomitant additions of large amounts (500 to 1000 μg) of UDP N-acetylglucosamine were not successful.

**DISCUSSION**

The results of this study are consistent with the view that steroids, like drugs and foreign chemicals, stimulate porphyrinogenesis in liver cells by enhancing the synthesis de novo of δ-aminolevulinic acid synthetase, the initial and rate-limiting enzyme in heme biosynthesis. In addition, this study raises the possibility that part or all of the glucose repression of experimental porphyria (15) may be accounted for by the glucuronidation and thus inactivation of inducers of ALA-synthetase, via the glucose-UDP-glucuronic acid-transglucuronate pathway.

**Similarity of Steroid and Drug or Chemical Induction of Porphyrin Synthesis** It was previously shown that porphyrin-inducing drugs and foreign chemicals act by stimulating the synthesis de novo of ALA-synthetase in the liver (3, 4). This was established by direct measurement of the enzyme activity in the induced livers of whole animals such as the guinea pig (3), the chick embryo (4), and the rat (16), as well as by the data obtained in studies on the mechanism of porphyrin induction in chick embryo liver cells in culture (4). In this and in the preceding paper (2), the induction caused by natural steroids in respect to its time characteristics and its response to various inhibitors of induction has been shown to be entirely similar to that caused by various chemicals and drugs. The additive inducing effects of suboptimal amounts of steroids and AIA, as well as the failure of combined optimal amounts of these agents to intensify the induction process or to significantly shorten its latent period support the idea that natural steroids and foreign chemicals or drugs act at the same cellular site.

The studies with inhibitors of nucleic acid and protein synthesis, such as actinomycin D, puromycin, and related agents (Table II) provide strong evidence that steroid induction of porphyrinogenesis in liver requires the formation of new RNA and an intact protein-synthesizing apparatus. These results are interpreted to mean that natural steroids, like drugs and other porphyria-inducing chemicals, induce the formation de novo of ALA-synthetase. The ability of heme and other metalloporphyrins to block the steroid-induction process further supports the view (1) that heme and steroids may be competing for a binding site on a repressor protein (see below).

**Steroid Induction, Blocking Effect of UDP-glucuronic Acid, and "Glucose Repression" of Porphyrin**—The ability of even potent steroids to induce porphyrinogenesis was entirely blocked by...
their conjugation with glucuronic acid as described previously (1, 2, 17). In the present study, it was found that UDP-glucuronic acid, the immediate donor of glucuronic acid in conjugation reactions catalyzed by UDP-glucuronoyltransferase, also blocked steroid induction. This effect is considered to reflect the conversion of the free steroid inducer to the inactive glucuronide conjugate by the added UDP-glucuronic acid. The chick embryo liver has been shown to possess a low activity of UDP-glucuronoyltransferase (18), and the enhancement of glucuronidation by UDP-glucuronic acid is well known (14). The large amounts of UDP-glucuronic acid required for blocking steroid induction probably reflect a relative impermeability of the cell to the nucleotide and the rapid hydrolysis of UDP-glucuronic acid by microsomal pyrophosphorylase (14).

The feeding of large amounts of glucose to animals has been found to inhibit the porphyria induced by certain chemicals (15, 19). This has been referred to as the "glucose effect" on ALA-synthetase. It has been emphasized (15) that this glucose effect may have no relation to the phenomenon of "catabolic repression," i.e. the ability of glucose in bacteria to repress the formation of certain inducible enzymes. The inhibitory influence of added UDP-glucuronic acid on steroid induction of porphyrins raises the possibility that glucose repression of porphyria in animals may be accounted for, in part or perhaps in whole, by conversion of the administered sugar to UDP-glucuronic acid which then leads to enhanced glucuronidation, and thus inactivation, of inducing substances. The inhibitory effects of high carbohydrate diets on porphyrin production in human porphyria (20) may have the same basis. Glucose repression of porphyrin induction by steroids has not as yet been demonstrated in the chick embryo liver culture system in vitro. This may be due to limiting concentrations of important intermediates or enzymes in the glucuronic acid pathway. Chick embryo liver does appear to synthesize small amounts of UDP-glucuronic acid and has detectable levels of UDP-glucuronoyltransferase activity, but these are present in substantially smaller amounts than are found in adult fowl (18).

**Working Hypothesis of Mechanism of Steroid Induction**—It is suggested as a working hypothesis that inducing steroids control formation of ALA-synthetase, the limiting enzyme in heme formation, by the mechanism depicted graphically in Fig. 1. This hypothetical mechanism is based on the model for drug induction of porphyria presented earlier from this laboratory (4, 21, 22). Control of porphyrin and heme synthesis in liver is considered to reside in a repressor-operator mechanism which regulates the activity of the structural gene (G) which codes for the rate-limiting enzyme (E), ALA-synthetase. All other enzymes in the heme biosynthetic chain (E to E) are present normally in non-limiting amounts. The repressor comprises an aporepressor protein to which a co-repressor, heme, the end product of the synthetic pathway, is bound. The repressor is inactivated by chemicals which compete with heme for its binding site on the aporepressor protein. Inactivation of the repressor leads to "derepression" of the structural gene for ALA-synthetase, enhanced formation of this rate-limiting enzyme, and increased production of heme, as well as of the intermediate porphyrins and precursors in this biosynthetic pathway. As formulated in Fig. 1, the concentration of active steroid inducers in the hepatic cell would depend, among other factors, on the rate of their conversion by UDP-glucuronoyltransferase to the inactive glucuronides, and on the rate of hydrolysis of the glucuronides back to the active free steroids by β-glucuronidase. The potential activity of inducing steroids would terminate only with their excretion.

**Possible Clinical Implications of Steroid Induction of Porphyrin Synthesis**—There is considerable clinical evidence which suggests that endocrine substances may play a role in the pathogenesis of hepatic porphyria in certain patients. Thus the acute intermittent form of the disease, even though transmitted as an autosomal dominant trait, has a high female preponderance. Hepatic porphyria occurs almost exclusively at postpubertal ages. A clear history of attacks may be elicited in some women in relation to specific phases of the menstrual cycle, and onset or exacerbation of the disease has been noted during pregnancy. Finally the administration of natural and synthetic hormones has been shown to enhance porphyrin-precursor excretion in normal subjects and to provoke chemical and symptomatic relapse of porphyria in patients with both the acute intermittent and the hepatic-cutaneous or acquired form of the disease (23-27). In light of these clinical observations and the physiological origin of the strongly active porphyrin-inducing steroids described in the previous paper (2), it is considered probable that steroids represent one class of endogenous agents which periodically exacerbate hepatic porphyria in some patients.

The role of steroids as provocative agents in the pathogenesis of hereditary hepatic porphyria would be contingent on the quantity of unconjugated steroid inducers which gained access to the inducing site or sites in the liver (Fig. 1). Thus any process such as starvation or glucose restriction (28) which impaired the glucuronidation of steroids or enhanced intracellular hydrolysis of steroid glucuronides by β-glucuronidase might lead to the accumulation of inducing steroids in liver cells in concentrations sufficient to stimulate further excess porphyrinogenesis in subjects carrying the genetic lesion of this disease. Excessive production of inhibitors of UDP-glucuronoyltransferase could also lead to the accumulation of high concentrations of inducing steroids in liver cells. In this respect, it is of interest that certain porphyrin-inducing 5β-H steroids themselves, such as pregnanediol may inhibit the activity of UDP-glucuronoyltransferase in

**Fig. 1. Schema depicting a proposed mechanism for steroid control of porphyrin and heme biosynthesis. None of the positions of the genes in the genome are known. This schema is presented as a working hypothesis. UDPGA, uridine diphosphate glucuronic acid.**
liver as shown by Lathe and Walker (29) and others (30, 31). This raises the theoretical possibility of the development of a cycle in which such steroids, having accumulated in the liver cell in sufficient concentration, would inhibit UDP-glucuronyltransferase, leading to further accumulation of more unconjugated porphyrin-inducing steroids, which would further inhibit steroid glucuronidation, and so forth. Termination of such a cycle might then depend in part on compensatory enhancement of alternative modes of conjugation and excretion of steroids or on chemical transformation of steroids to more highly oxygenated, inactive, or more easily disposable derivatives, a process which may be favored by the large amounts of heme and heme-proteins such as cytochrome P-450 being formed by the liver in the induced state (32). Patients carrying the genetic lesion (i.e., mutant operator) for hepatic porphyria would be especially susceptible to the inducing action of endogenous steroids as described here. However, even in normal subjects, steroids may enhance porphyrin-precursor excretion (27) and chemical and drug-induced porphyria may be evoked in normal man (33) as well as in normal experimental animals (3) under appropriate conditions. It is therefore possible that the inducing effect of endogenous steroids could also be reflected in the porphyrinurias which characterize certain patients with acquired types of liver disease, such as hepatic cirrhosis, in which steroid conjugation is known to be impaired and elevated levels of ALA-synthetase have recently been demonstrated (34).

REFERENCES

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