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EFFECT OF ESTROGENS ON THE LIVER

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Although the liver is not generally regarded as a target organ for estrogens, several clinical observations and a number of physiological studies suggest that it is. The identification of estrogen receptors in liver cytosol and nuclei support this conclusion.[1, 2] We shall discuss several of the more important physiological and clinical effects of estrogens upon the liver (table 1) and shall illustrate them by brief case reports.

Case Presentation

WILLIAM ERFLING, M.D.

S. C., a 20-year-old, nulliparous white female was given Librium (chlordiazepoxide) and Enovid (mestranol 0.16 mg, norethynodrel 10 mg) because of anxiety and irregular menses in 1963. Five days later pruritus began and persisted; 3 weeks later jaundice appeared. Medications were discontinued, but pruritus and jaundice, associated with an elevated serum alkaline phosphatase level, led to an exploratory laparotomy. The liver, gallbladder, and bile ducts appeared normal except for a solitary 2.5-cm stone in the gallbladder. A cholecystectomy was done. Liver biopsy showed centrilobular bile stasis only. She was well until June 1964 when she was given Enovid again and within 5 days developed pruritus and jaundice. Apercutaneous needle liver biopsy showed cholestasis. Liver function tests were compatible with cholestasis. The drug was stopped and she recovered promptly.

There was no past medical history or family history of jaundice or pruritus during pregnancy.

In June 1965 she was first seen at Colorado General Hospital. Her serum glutamic oxalacetic and glutamic pyruvic transaminases, bromsulfophthalein (BSP) retention, and other liver tests were normal. An intravenous cholangiogram was also normal. She was challenged with the estrogen, mestranol, 0.16 mg per day, and on the 5th day developed an elevated serum bilirubin and alkaline phosphatase level and increased BSP retention 45 min after a standard dose.[3] Maximum transport of BSP was reduced and storage capacity was increased. Liver biopsy showed only canalicular bile plugs. Challenge with the progestational agent, norethynodrel, 10 mg per day for 14 days, produced fatigue only.

In 1968, she became pregnant and remained well until pruritus gravidarum developed during the latter part of the third trimester.

Effects of Estrogens on the Liver

FRANCIS R. SIMMON, M.D.

The effects of estrogenic components of oral contraceptives on the liver have received increasing attention because of their association with abnormal liver function, formation of cholesterol gallstones, and their possible relationship to hepatic cancer. My presentation will emphasize three points about oral contraceptives. (1) They cause a predictable and reversible reduction in hepatic excretory function, primarily owing to the estrogenic component. (2) Jaundice occurs primarily in those

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TABLE 1. *Principal effects of estrogens upon the liver*

Physiological effects
Decreased bile flow
Diminished secretion of organic anions
Diminished bile acid synthesis and secretion
Clinical syndromes
Pruritus gravidarum, intrahepatic cholestasis of pregnancy
Cholesterol gallstones
Hepatic adenomas, benign nodular hyperplasia[a]

[a] There is controversy about the nature of the relationship between adenomata and hyperplasia and estrogen. See text.

patients with inheritable or acquired reduction in hepatic excretory function. (3) In animals, the effect of estrogens on hepatic excretory process provides insight into the normal physiology and biochemistry of bile formation.

Oral contraceptives are a combination of synthetic estrogens and progestogens, with the latter compound always present in much higher concentrations. Studies in animals have shown that specific structural features in the steroid nucleus and side chain are required to cause abnormalities in liver functions.[4] Decreased clearance of BSP is primarily related to the presence of a phenolic A ring, whereas potency is accentuated by the addition of 17 α-alkyl substitution. Both of these properties are present in synthetic estrogens, ethinyl estradiol, and mestranol, which are used in oral contraceptives. Progestogens, on the other hand, are derivatives of either 19-nortestosterone or progesterone. Synthetic progestogens derived from 19-nortestosterone also contain a 17 α-alkyl substitution. Decreased hepatic excretory capacity and abnormal liver function tests have been reported only with these progestogens. These effects may result from metabolism of 19-nortestosterone progestogens to estrogens, rather than a direct effect of the progestogen itself.

The difference in potency between mestranol (estrogen) and norethynodrel (progestogen) is clearly shown in the patient presented here. Abnormal liver function tests were produced by administration of the oral contraceptive containing both mestranol and norethynodrel and by the estrogenic component alone, but not the progestogen alone. These observations emphasize that the major cause of abnormalities associated with oral contraceptives is apparently related to the estrogenic component of the pill, although progestogens may play an additional role.[5]

In most asymptomatic individuals taking oral contraceptives the serum bilirubin, transaminase, and alkaline phosphatase activities are normal or only minor transient elevations are observed. The significance of these alterations is uncertain for their frequency in a controlled population is unknown. However, the changes appear to be more marked and constant in postmenopausal women.[6]

In contrast to these variable effects on liver function tests a predictable reduction in BSP excretion is observed when hepatic storage and the maximum biliary excretion (*Tm*) are determined. Clearance of BSP from the blood involves uptake of the dye and hepatic storage, intracellular conjugation with gluthathione, and subsequent excretion into bile by a rate-limiting transport process. In hepatic disease both storage and BSP *Tm* are reduced. However, in patients receiving oral contraceptives only BSP *Tm* is reduced approximately 50%, whereas storage capacity is either unaltered or slightly increased.[7] This effect of oral contraceptives is mimicked by the administration of large doses of the natural estrogen, estradiol. Thus, the estrogenic component of oral contraceptives predictively and also reversibly reduces hepatic excretory function.

Why does pruritus or jaundice develop in some subjects and not in others? Current evidence suggests that the majority of individuals who develop jaundice from oral contraceptives have reduced biliary excretory capacity before drug ingestion.[8] The normal liver has a large excretory capacity reserve, and a reduction of 50% generally is not associated with jaundice. This is illustrated in figure 1 where the maximum capacity of rats to excrete bilirubin is compared to serum bilirubin levels.[9] Many steroids are capable of reducing bilirubin transport capacity, but serum bilirubin levels do not become abnormally increased until excretory capacity is reduced below 10% of control. Thus, if similar hepatic excretory reserve exists in man, preexisting abnormalities in biliary excretion must exist before jaundice will appear after oral contraceptive use.

Approximately 50% of patients developing jaundice with the use of oral contraceptives have intrahepatic cholestasis of pregnancy, a disorder which was first described in detail in 1954. Although it has a worldwide distribution, it is most common in Chile and the Scandinavian countries. Because no specific tests are available, intrahepatic cholestasis of pregnancy is diagnosed by its clinical features. It usually appears in women in the second half of the pregnancy, and is characterized by severe pruritus, mild jaundice, and "cholestatic" liver function tests. All these abnormalities rapidly disappear in the first days postpartum. The term pruritus gravidarum is applied to pregnant women complaining of persistent itching, and who also have "cholestatic" liver function abnormalities but without jaundice. Pruritus gravidarum and intrahepatic cholestasis of

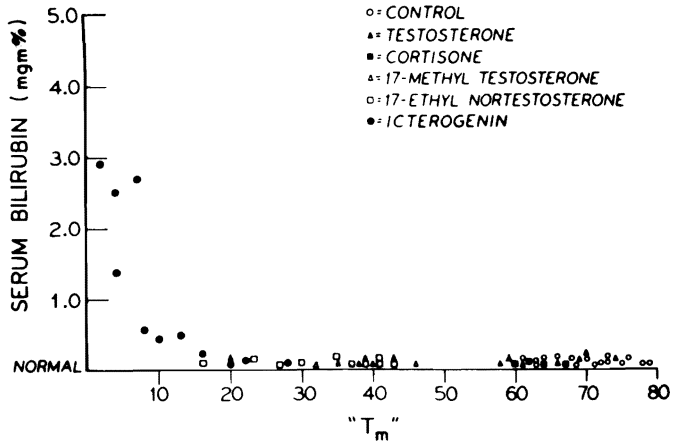

FIG. 1. Relationship between hyperbilirubinemia and bilirubin excretory maximum ("*Tm*") in Wistar rats treated with various steroids and icterogenin.[9]

pregnancy may alternate in different pregnancies in the same women, and thus both are considered different clinical forms of the same disease. Neither functional nor histological sequelae have been described for either clinical syndrome. Although genetic factors are considered important in its pathogenesis, the cause of intrahepatic cholestasis of pregnancy is unknown. Challenge studies with hormones, as in our patient discussed here, suggest that patients are abnormally "sensitive" to estrogens. Rather than causing an increased response, cholestasis may result from further reduction of an already decreased hepatic excretory capacity for organic anions. Oral contraceptives increase serum bilirubin, but not bile acids, in the Dubin-Johnson syndrome, a selective disorder in bilirubin excretion.[8] In addition, hyperbilirubinemia is increased by oral contraceptives in patients with cirrhosis. Although a constitutional defect in BSP transport is likely to be present in intrahepatic cholestasis of pregnancy, it has not been specifically identified. However, the effects observed in Dubin-Johnson syndrome and cirrhosis support the hypothesis that oral contraceptive-induced cholestasis in most cases depends upon an underlying abnormality in hepatic excretion of organic anions.

The effect of ethinyl estradiol on the hepatic transport of bile acids has been examined in detail, for this is the major organic anion excreted into bile. Studies in man and rats are consistent with a diffuse effect of estrogen on the bile canalicular membrane and/or the presumed carrier molecules for organic anions. A number of investigators have shown that administration of ethinyl estradiol to rats does not alter basal bile acid excretion,

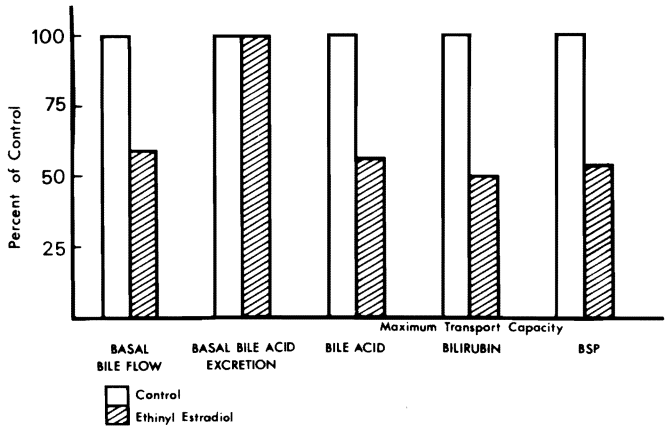

FIG. 2. Effect of ethinyl estradiol administration (5 mg per kg per day × 5 days) on bile flow, basal bile acid excretion, and maximum capacity to excrete organic anions.

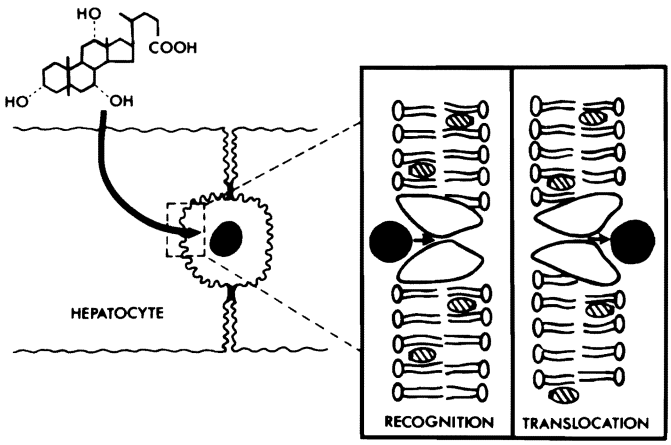

FIG. 3. Schematic model of hepatic transport of bile acids.

but decreases hepatic transport of biliary water, and the maximum capacity to excrete organic anions, such as bile acids, bilirubin, and BSP (fig. 2).

Bile acids are transported across both sinusoidal and canalicular membranes by a carrier-mediated process shown schematically in figure 3. Optimal membrane transport is dependent upon both the numbr of putative bile acid carriers, and the fluidity of the membrane lipid bilayer which apparently permits the carrier to undergo movement. In spite of a reduction in bile acid transport to 65% of control, the number of putative carriers was unchanged by ethinyl estradiol treatment.[10] Abnormal transport after ethinyl estradiol treatment is associated with decreased membrane lipid mobility, probably the result of an increased content of cholesterol in liver surface membrane fractions.[11] This change in membrane lipid physical structure found in animal studies suggests similar changes in canalicular membranes may occur with oral contraceptive use in humans and thus account for decreased hepatic transport of organic anions.

In conclusion, oral contraceptives cause a dose-related, predictable, and reversible abnormality in hepatic excretory function in humans and experimental animals. The estrogenic component, which contains both a phenolic A ring and a 17 α-alkyl substitution, is apparently the major cause of liver functional abnormalities, particularly in patients with either genetic or acquired forms of reduced biliary secretory capacity. Finally, animal studies suggest that estrogens may cause abnormal hepatic transport of organic anions by alteration of membrane lipids, rather than by decreasing the number of putative carrier proteins.

Cholesterol Gallstones

FRED KERN, JR., M.D.

Cholesterol cholelithiasis is more common among women than men in every population that has been studied (fig. 4). This difference between men and women begins during puberty (fig. 5) and is present throughout the childbearing years, focusing attention upon the effects of female sex hormones. The administration of

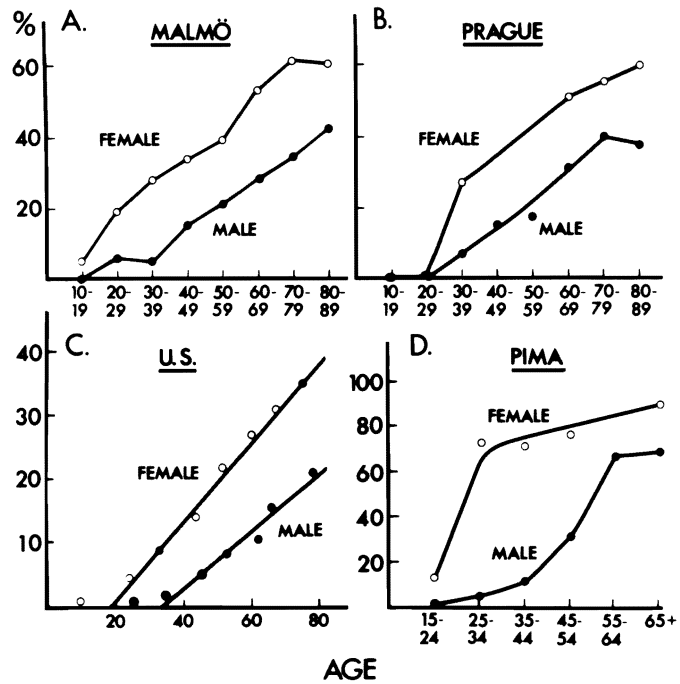

FIG. 4. Incidence of gallstones in four different population groups. Note the increase in females during the child bearing years. The data from Malmö and Prague[12] and the United States[13] are based upon autopsy studies. The Pima Indian study was based upon clinical and cholecystographic data.[14]

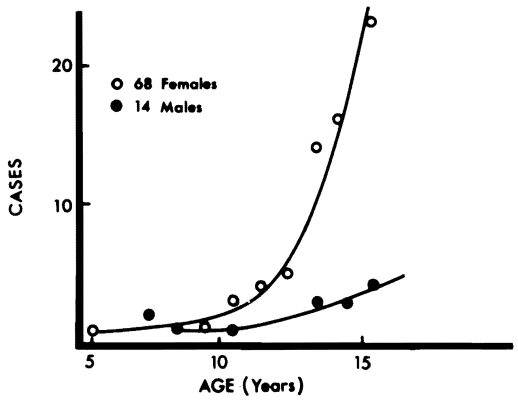

FIG. 5. Cholelithiasis in children in a Swedish community hospital, reproduced from *Acta Chirurgica Scandinavica*[15] with permission. Note the increase in number of female cases at the time of puberty.

oral contraceptive steroids to premenopausal women doubles the incidence of cholesterol cholelithiasis. The administration of estrogens to postmenopausal women (fig. 6) and to men has similar effects.[17, 18] Parity is possibly directly correlated with the incidence of gallstones. Among women who have had intrahepatic cholestasis of pregnancy, gallstones develop in later life twice as frequently as among matched controls.[19] The pathogenesis of stone formation in these various groups has not been fully explained, but all of these observations emphasize the importance of female sex hormones.

Cholesterol gallstones are 60 to 90% cholesterol. The initial step in their formation is the production of an abnormal bile; that is, bile containing excess cholesterol. The normal relative molar percentage of the major organic components of bile—bile acids, lecithin, and cholesterol—is 70–85:10–25:5–10, respectively. Cholesterol is held in solution in the bile in mixed micelles of bile acids and phospholipids. The molar proportion of bile acids plus lecithin to cholesterol is 15–20:1. When the ratio falls to 10:1 or less, excess cholesterol is present in supersaturated solution and, when bile in the gallbladder is "seeded" by precipitated pigment or other solid matter, cholesterol crystals precipitate out of solution and initiate gallstone formation. Such bile is known as lithogenic.

The possible mechanisms leading to the production of lithogenic bile are shown in table 2 and will be briefly discussed. They may be disorders of hepatic or gallbladder function or both.

Excess hepatic cholesterol secretion clearly occurs in obesity[20] and is proportional to excess weight in the morbidly obese.[21] In less obese patients the relationship between biliary cholesterol secretion and percentage of body fat has not been carefully examined in a large number of patients. Evidence indicates that the major abnormality associated with estrogen administration is decreased bile acid synthesis and secretion. Lecithin synthesis and secretion is secondary to bile acid secretion. When bile acid secretion is reduced, lecithin secretion is reduced.[22, 23] (A primary defect in hepatic lecithin metabolism has not been described.) Cholesterol secretion is less dependent upon bile acid secretion as shown diagramatically in figure 7. Thus, decreased bile acid secretion leads to lithogenic bile because relatively more cholesterol is secreted.

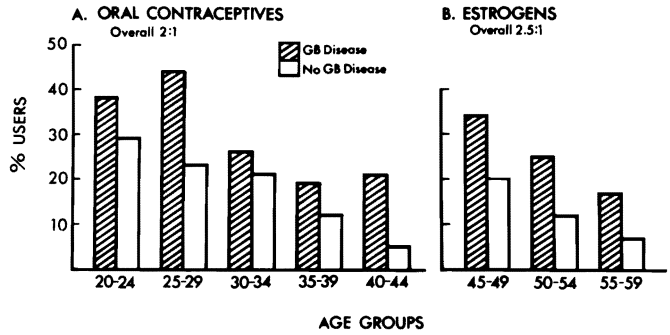

FIG. 6. Frequency of oral contraceptive (*A*) and estrogen (*B*) use among patients with surgically proven gallbladder disease and among matched controls. The women who used these agents had gallbladder (*GB*) disease 2 to 2.5 times more frequently than the controls who did not use them. Modified from studies by the Boston Collaborative Drug Surveillance Program.[16, 17]

TABLE 2. *Possible mechanisms of production of bile containing excess cholesterol*

Hepatic
Excess cholesterol secretion
Decreased bile acid synthesis and secretion
Decreased lecithin secretion
Gallbladder
Selective absorption of bile acids and/or lecithin
Defective emptying

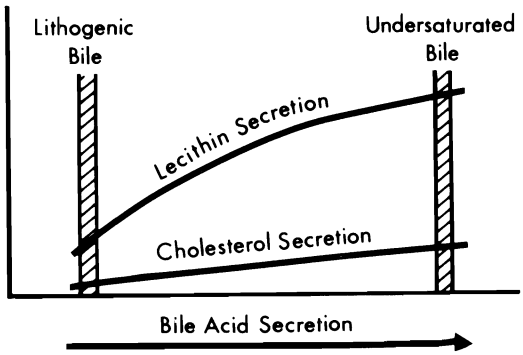

FIG. 7. Schematic representation of the relationships between bile acid secretion and the secretion of lecithin and cholesterol in the bile. At low rates of bile acid secretion the bile is lithogenic because there is relatively more cholesterol than bile acid or lecithin.

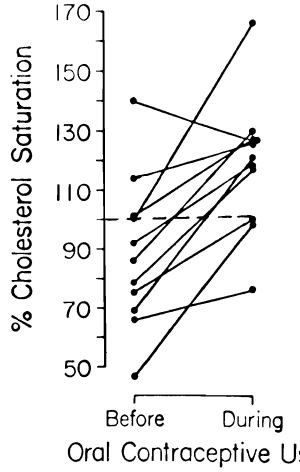

FIG. 8. Effect of oral contraceptive administration for 3 weeks upon cholesterol saturation of bile, obtained from the duodenum after gallbladder stimulation. *Dashed horizontal line* represents 100% saturation. *Points* above that line indicate supersaturated bile. Saturation with cholesterol increased in 10 of 11 patients. Reproduced with permission from L. J. Bennion, et al., and from *New England Journal of Medicine*.[24]

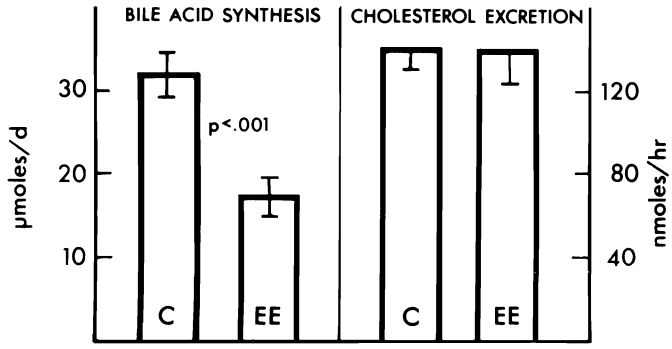

FIG. 9. Effect of ethinyl estradiol (5 mg per kg per day × 5) on bile acid synthesis and biliary cholesterol secretion in the biliary fistula, bile acid-depleted rat. Bile acid synthesis is approximately half that of the control, but cholesterol secretion is unaffected, resulting in bile that is more saturated with cholesterol. *C*, control; *EE*, ethinyl estradiol-treated.

Studies of the effects of estrogens upon biliary lipids show the following. (1) In women taking contraceptive steroids, the bile becomes lithogenic[24] (fig. 8). (2) In a single study of 3 women with a T-tube in the common bile duct, the administration of Premarin and Provera caused a decrease in cholic acid synthesis and pool size and an increase in the molar percentage of biliary cholesterol in the bile.[25] (3) In rats[26–28] and hamsters[29] given ethinyl estradiol, bile acid synthesis and secretion decrease and biliary cholesterol secretion does not change (fig. 9). The bile, therefore, contains relatively more cholesterol. (4) In hamsters, ethinyl estradiol decreases the activity of cholesterol 7 α-hydroxylase, the enzyme that is rate limiting for the conversion of cholesterol to bile acids.[29] (5) In the rat, ethinyl estradiol affects the lipid composition and physical characteristics of the hepatic microsomal membrane, which is the site of the critical steps in conversion of cholesterol to bile acids.[27, 30] The principal change in lipid membrane composition is an increase in concentration of both free cholesterol and esterified cholesterol. Cholesterol esters, which do not serve as substrate for bile acid synthesis, are synthesized in the hepatic microsomal membranes, regulated by cholesterol acyl CoA transferase, the cholesterol esterification enzyme. Increased activity of this enzyme seems to be a primary effect of estrogens, both in vitro and in vivo.[30, 31] Decreased activity of cholesterol 7 α-hydroxylase, a microsomal membrane-bound lipid phase enzyme, could be secondary to changes in membrane lipid composition. Bonorris et al.,[29] however, failed to find an increase in cholesterol of the hepatic microsomal fraction in their hamsters treated with ethinyl estradiol, even though, as noted, cholesterol 7 α-hydroxylase activity was decreased.

The possibility of altered gallbladder function in response to estrogens has been incompletely studied. There is selective absorption of bile acids from the diseased gallbladder mucosa, but not from a normal gallbladder mucosa.[32, 33] A diseased gallbladder mucosa, therefore, may perpetuate the conditions leading to stone formation, but absorptive defects probably do not play a role in initiating the process. Effects of estrogens upon gallbladder storage capacity and contractility have not been well characterized. A defective response to stimulation has been described during various phases of the menstrual cycle[34] and recent studies have shown poor contractility of the gallbladder during pregnancy.[35] If estrogens or progestogens did produce poor contractility of the gallbladder, there could be prolonged storage of the bile acid pool in the gallbladder and diminished enterohepatic cycling of bile acids. This might decrease the biliary secretion of bile acids and lecithin, and because cholesterol secretion would not be decreased proportionately, the bile would become more saturated with cholesterol. Much remains to be learned about the effects of female sex hormones on the metabolism of bile acids and cholesterol and about biliary physiology.

Case Presentation

ROBERT DAHL, M.D.

A 26-year-old white woman presented with 4 hr of nausea, vomiting, and right upper quadrant pain which was severe and radiated to the shoulders. Three months earlier similar pain occurred and resolved spontaneously. There was no history of jaundice, fever, chills, or any type of liver disease. She had used a sequential birth control pill 3 years before a recent pregnancy and shortly thereafter. Initial examination disclosed normal vital signs, right upper quadrant tenderness, and hypoactive bowel sounds. The liver and spleen could not be felt. A few hours after admission the patient suddenly became hypotensive and, after transfusions were started, a liver scan and celiac angiogram were performed; they suggested the presence of a mass in the right lobe of the liver. After stabilization she was transferred to Colorado General Hospital for surgery. A 12.5-cm hepatic adenoma in the right lobe of the liver had ruptured and bled intraabdominally. A trisegmentectomy was performed. The patient did well postoperatively and remains well 7 years later.

Hepatic Tumors and Oral Contraceptives

ANDREW MALLORY, M.D.

Since 1970, evidence has been growing that oral contraceptives may cause a variety of liver tumors. This evidence includes: (1) a large number of case reports of both benign and malignant tumors in women taking oral contraceptives; (2) reports of regression of tumors after cessation of oral contraceptive therapy;[36, 37] (3) recurrence of tumors after surgical resection in patients continuing to take oral contraceptives.[38] In addition, Edmondson et al. have recently reported increased duration of oral contraceptive use among patients with hepatic tumors when compared with matched controls.[39] Although most of this evidence is circumstantial and has been disputed[40] and the results of animal experiments are conflicting,[41] the evidence on balance strongly suggests a causal association between these drugs and hepatic tumors.

Klatskin has recently reviewed the clinical details of 117 cases described in the literature.[41] The data that follow come largely from that review.

The types of hepatic tumors reported are listed in table 3. Ten reported tumors have been malignant. The smaller number of cases makes it more difficult to establish a causal relationship with oral contraceptives. These tumors, therefore, will not be discussed further.

The majority of tumors have been benign and classified as either hepatic cell adenomas (solitary, grossly smooth, and sharply circumscribed masses of normal-appearing hepatocytes) or focal nodular hyperplasia (firm, grossly nodular masses which on cross-section contain a central fibrous core with radiating septa that divide the tumor into nodules). Although this classification is generally accepted, many authors agree that some benign tumors may be difficult to classify.

The majority of women with benign tumors had taken contraceptives for more than 5 years. Ten per cent, however, had done so far less than 12 months and, in 7 per cent, the tumor was discovered 6 months to 10 years after cessation of contraceptive therapy. Presenting complaints are listed in table 4.

Physical findings consist of a right upper quadrant mass in those with large tumors and signs of shock or right upper quadrant tenderness in those who have bled into the tumor.

Laboratory results are usually normal. In Klatskin's review, serum bilirubin, alkaline phosphatase, and glutamic oxalacetic transaminase were mildly abnormal in 5, 30, and 30%, respectively; α-fetoprotein was normal in all 11 patients tested.

TABLE 3. *Types of hepatic tumors in women using oral contraceptives*[41]

Tumors	No. reported
Benign	
Hepatic cell adenoma	79
Focal nodular hyperplasia	28
Malignant	
Hepatocellular carcinoma	8
Hepatoblastoma	1
Mixed hepatocellular-ductular	1

TABLE 4. *Presenting complaints in women with benign hepatic tumors*[41]

Symptom	Hepatic cell adenoma	Focal nodular hyperplasia	Total
Acute abdominal pain and shock	53 (68)[a]	6 (21)	59 (55)
Palpable mass	18 (23)	4 (14)	22 (21)
Chronic or intermittent pain	1 (1)	4 (14)	5 (5)
Asymptomatic	7 (9)	14 (50)	21 (20)

[a] Numbers in parentheses are percentage of total in group.

Radiological findings are frequently abnormal but not specific. Technetium liver scans showed filling defects in 81% of patients tested. Arteriograms were abnormal in 90%.[41]

The natural history of these tumors has not been adequately studied because most patients undergo surgical resection. Of 12 tumors left in situ, four have shown regression in size in patients discontinuing contraceptive therapy. In none of these tumors has there been evidence of progression or malignant transformation.

Surgical Treatment of Hepatic Adenoma and Focal Nodular Hyperplasia

THOMAS STARZL, M.D.

There is very little to add to what you have just heard, which was an excellent review. I would like to tell you about the case material that we have accumulated at the University of Colorado. Seven patients have had hepatic resection for adenomas. The first of these cases was misdiagnosed. Although Dr. Dahl was kind enough not to point it out, the patient whose course was presented actually was signed out as having a hepatoma. She was placed on 5-flurouracil therapy for about 3 postoperatively years. The same applied to the second and third cases. These errors were not picked up until the report by Baum et al.[42] The surgical specimens eventually were reexamined by Dr. Hugh Edmondson of Los Angeles and by Dr. Fennell of our own pathology department, leading to reclassification.

I would like to focus on the critical question which was raised about the association of the adenomas with birth control pills. Of the 7 patients at the University of Colorado who came to operation, 3 did not have an obvious association between the pill and their tumors. One was a 14-year-old girl. She had been exposed to the pill onlyfor about 1 week, less than 1 year previously. The 2nd patient was a 17-year-old woman who had never been on the pill. The 3rd patient was a male.

Those of you in the audience who are skeptical of the pill hypothesis will be interested in an article by Guzman et al.[40] which contains a persuasive argument against the pill association.

In considering the appropriate treatment of hepatic adenoma, it is important to appreciate that upwards of 70% of these typically young ladies present with acute intraabdominal hemorrhage. The results may be devastating. Berg, an oncologist at the University of Iowa, surveyed that state's public health records for a number of years and found 4 cases of hepatic adenoma, all in woman who bled to death.[43] This kind of study has influenced us to recommend operation for these patients, particularly because the lesions have been very

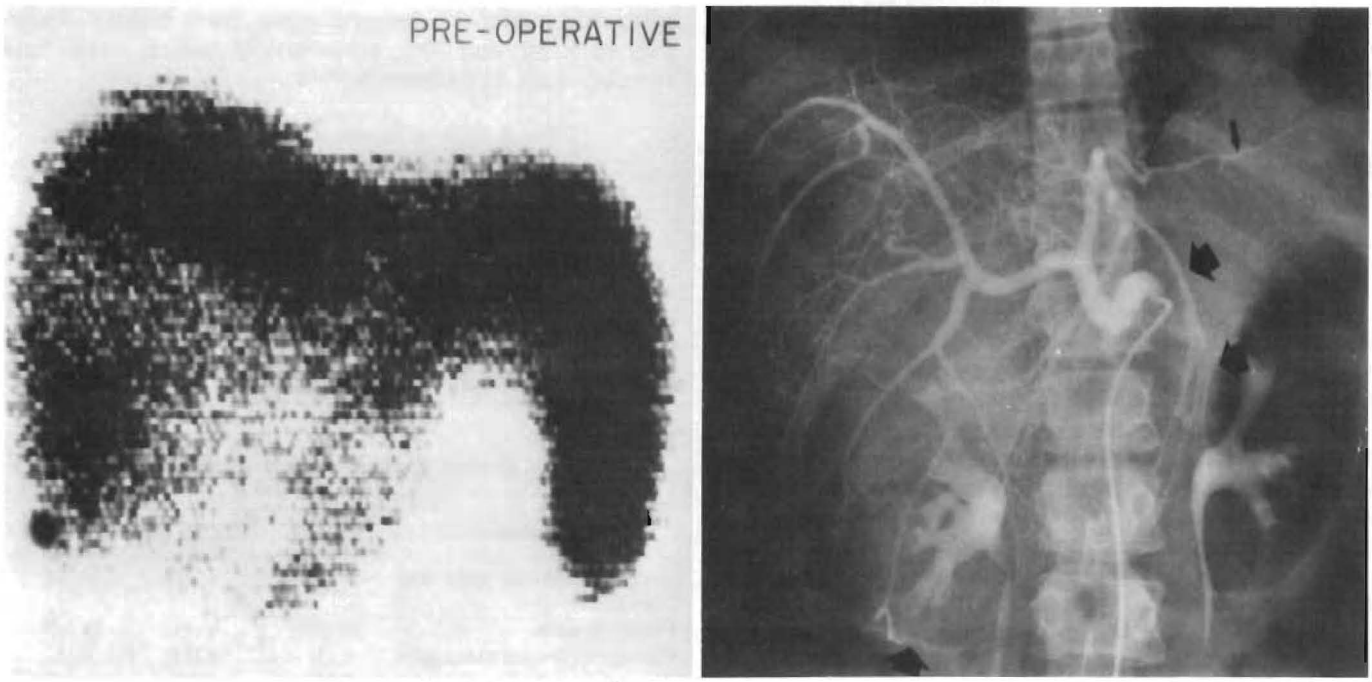

FIG. 10. Preoperative radiographic studies. *Left,* 99m technetium liver scan (anteroposterior projection) showing a very large filling defect. *Right,* selective common hepatic arteriogram. *Broad arrows* indicate the extent of the tumor as outlined by the abnormal configuration of vessels. *Thin arrow* points to the dorsolateral branch of the left hepatic artery. This vessel, supplying the lateral segment of the left lobe, was the only hepatic arterial branch preserved. (By permission of *American Journal of Surgery* 129:587–590, 1975.)

large in our cases and ruptured in three instances.

Dr. Mallory has covered the work-up of patients with suspected adenomas. Angiography is very helpful, not only for diagnosis but also in planning the operation (fig. 10). Obviously the ultimate diagnosis in these cases is usually made either by needle biopsy or preferably at laparotomy.

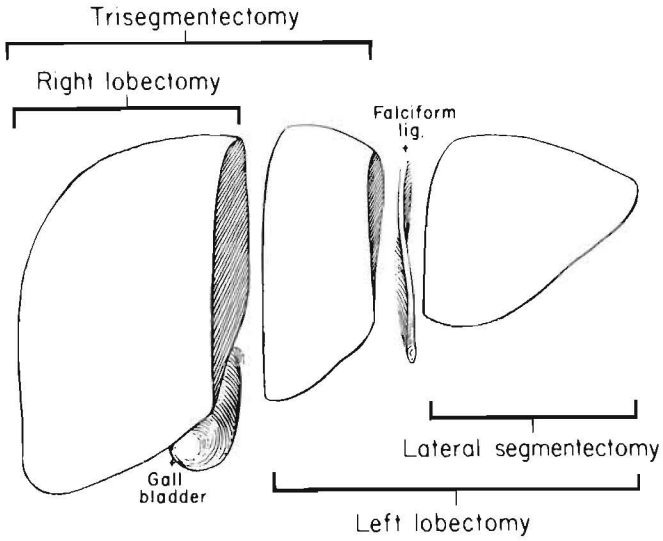

FIG. 11. Common hepatic resections of which there are only four. The most radical procedure, trisegmentectomy, involves removal of the true right lobe plus the medial segment of the left lobe. The least radical procedure, lateral segmentectomy, was incorrectly termed left lobectomy in the older literature.

To return now to treatment. One possibility is withdrawal of the estrogenic treatment, but obviously this could not be done if there were no estrogen treatment, as in almost half of our own cases.

I believe that resection should be carried out in a very formal way in which one or more anatomical segments are removed, as opposed to piecemeal removal of the tumors as has been recommended by some authorities. Figure 11 shows the anatomical units that I believe can be safely resected.[44] Formal right lobectomy or formal left lobectomy consists of two segments. There is the possibility of performing a so-called extended right hepatic resection (trisegmentectomy) which involves removal of three full segments or about 80 to 85% of the liver mass. This has been necessary in the treatment of 3 of our 7 patients, including the patient presented, leaving only the small left lateral segment. The fourth possibility is removal of the left lateral segment, which used to be known as the left lobe because it is the liver tissue to the left of the falciform ligament.

The 7 patients in the Colorado series were treated with extended right hepatic resection in three instances, standard right hepatic lobectomy in 3 more cases, and a left hepatic lobectomy in the other case.

These seven resections for adenoma were part of a

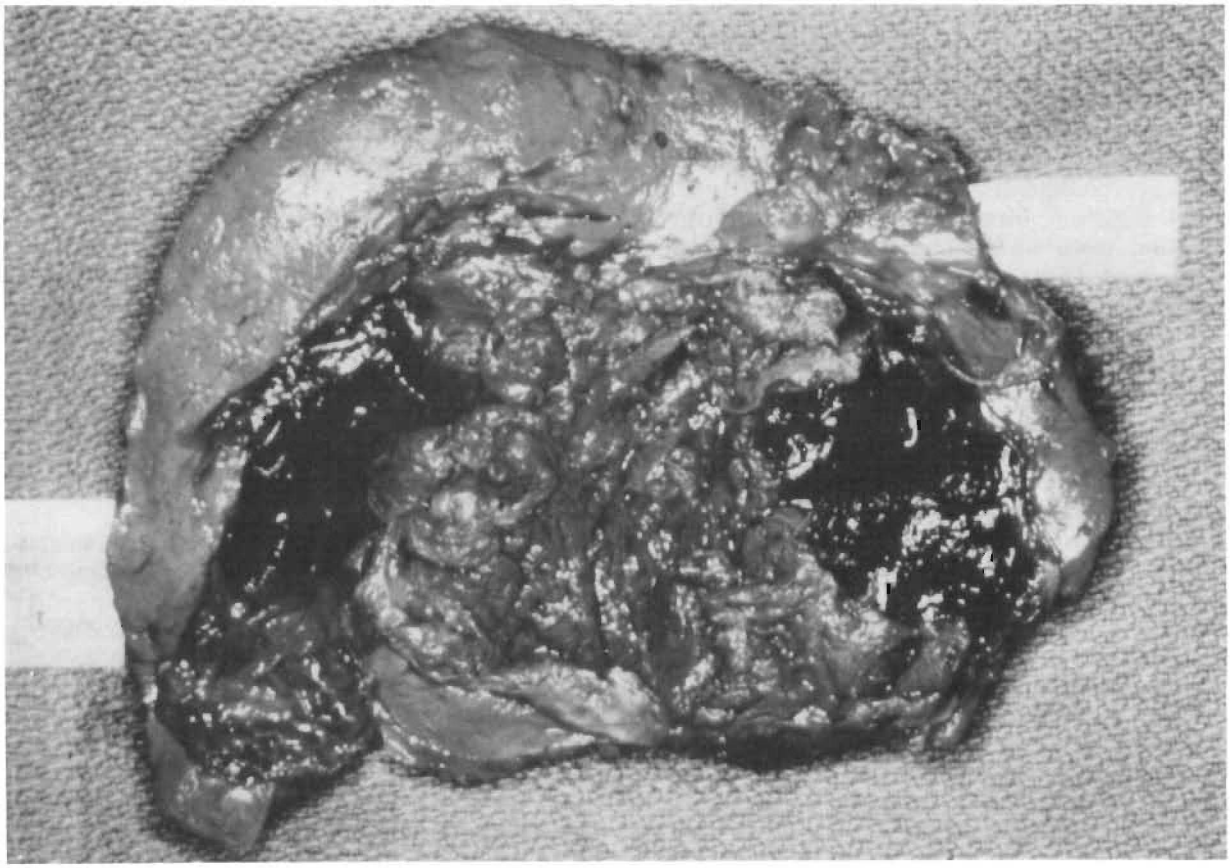

FIG. 12. Specimen from a 17-year-old girl with a huge hepatic adenoma. Hepatic resection (85%) was required. The case is the same as in figure 10.

total experience of 37 hepatic resections which I have performed or at which I assisted at the University of Colorado. There were no deaths in this group of 37. All 7 of the patients with adenoma are alive and well with follow-ups of 1 to 8 years. Obviously the operation is quite a safe one even when large quantities of liver must be removed (fig. 12). Therefore, surgical treatment can be applied somewhat more freely than if there were a high operative risk.

That concludes my remarks about hepatic adenoma. To complete the picture, I would like to mention separately our surgical experience with focal nodular hyperplasia. We have seen only 2 patients with this diagnosis whom we have submitted to resection. One had a lateral segment removed and the other had an 85% resection. However, my general recommendation for patients with focal nodular hyperplasia is not to operate because those patients do not frequently bleed as Mallory's citations of Klatskin's review[41] has demonstrated. Because it tends to be a quiescent lesion, I put focal nodular hyperplasia into a quite different category than the benign hepatic adenoma.

Discussion

Dr. Ernest Borek: We have observed recently that after the administration of three different carcinogens there is an effect which is germane to the subject of this conference. Ethionine, thioacetamide, and actinomycin D raise the progesterone level by as much as 10-fold above normal in the immature chick.[45] It is noteworthy that none of these carcinogens is positive in the Ames test. None of them is mutagenic. Whether there is any relationship between the production of this hormonal imbalance and carcinogenesis is under investigation.

Dr. Francis Simon: Both synthetic progestogens and estrogens in high doses have been shown in male and female rats to cause an increase over expected frequency of liver cell tumors.[46]

Dr. Ernest Borek: Carcinogenesis is highly species specific. Chronic administration of progesterone produces mammary tumors in the beagle. Moreover, administration of progesterone enhances tumor formation by dimethylbenzanthracene in the beagle.

Dr. Charles Scoggin: Do males receiving stilbesterol for prostatic carcinoma develop cholestasis?

Dr. Francis Simon: Minor transient abnormalities in liver function tests were noted in a small series of patients treated with estrogens for prostatic cancer. Similar to oral contraceptive use in women, the most consistent abnormality seen, in approximately 50% of the patients, was increased retention of BSP.[47]

Dr. Richard Bynny: What is the relationship between estrogen administration and the multiple venous lakes or dilated sinusoids in the liver?

Dr. Andrew Mallory: There is evidence that oral contraceptives or estrogens may affect the vasculature of benign tumors as well as the vasculature of normal liver tissue. In benign tumors, sinusoidal congestion, subintimal fibrosis and medical hypertrophy of medium-sized arterioles, and peliosis hepatis-like lesions have been described. In normal livers, several investigators have reported sinusoidal congestion[41] and at angiography, pooling of contrast material suggesting peliosis hepatis.[41, 48]

Dr. Fred Kern: Peliosis hepatis has been described in at least 2 or 3 patients receiving estrogens as well as in those receiving anabolic steroids.

Dr. Sunder Mehta: Is a percutaneous liver biopsy indicated or contraindicated when liver tumors associated with the "pill" are suspected.

Dr. Thomas Starzl: I would rather not have liver tumors biopsied in advance of resection. These patients should be operated upon once and by someone who can carry out a hepatic resection if that is indicated. Unfortunately, the usual situation in our series is that the patients have had needle biopsies or, more commonly, open biopsies. This creates a log of technical problems and is inconsistent with good oncological therapy if the liver mass proves to be a malignant tumor.

Dr. Karl Sussman: Do alterations in hepatic function and bile acid metabolism occur during the menstrual cycle?

Dr. Francis Simon: Except for BSP retention I do not know any evidence of alterations in liver function tests during the menstrual cycle. In some individuals retention of BSP at 45 min is apparently increased in the luteal and menstrual phases of the cycle.[49] However, BSP *Tm*, a more sensitive study, has not been examined during the cycle.

Dr. Fred Kern: Dr. Sussman's question is probably important, but there are few answers. There have been two studies of biliary lipid composition with conflicting findings. Biliary lipid composition was studied at three phases during the ovulatory cycle: at the time of menstruation, at the time of ovulation, and during the luteal phase. In the first study, biliary lipids were the same in all three phases.[50] In the second study the bile became lithogenic in the luteal phase.[51] Dr. Erfling and I are looking at this question in considerable detail at the present time.

Dr. Antonie de Torrente: Cirrhosis is associated with an increased incidence of gallstones. Is this because of alterations of bile acid metabolism?

Dr. Francis Simon: You are correct, but the increase is attributable to bilirubin stones, not to cholesterol gallstones.[52] It has been suggested that the pigment stones may result from increased hemolysis or another mechanism, rather than from alterations in bile acid metabolism.

Dr. Fred Kern: I would like to ask Dr. Mallory a question with regard to the controversy about whether benign hepatic adenomata are pill-related. It is, of

course, always extremely difficult to determine cause and effect in events that occur rarely, but I wonder if we get any useful information from the sex ratio of non-pill related cases?

Dr. Andrew Mallory: In the non-pill cases of benign hepatic tumors, Klatskin found that, of 138 cases reported, 124 or 90% were in women, most of whom were between the ages of 19 and 50. This propensity for tumor development in women of the childbearing age is further evidence supporting a hormonal relationship.

Dr. Thomas Starzl: I wish to add a detail about the Guzman study from Minnesota to which I referred earlier. The authors studied all of the case material from 1940 onward, and compared the prepill era with the pill era. There was no statistically significant difference in the incidence during these two times, but the tumors were bigger in more recent times. Consequently, Guzman et al., were willing to concede that the pill was an accelerator of growth. They were challenging the concept that it was an initiator of growth.

Dr. Andrew Mallory: They and others have also made the interesting observation that not only are the tumors larger in association with the pill, but also they seem to bleed much more frequently.

Dr. Robert Schrier: Dr. Starzl, could you comment on any derangements or complications which are associated with 85% hepatic resection, such as alterations in the renin angiotensin-aldosterone system, predisposition to lactic acidosis, or any other long term complications?

Dr. Thomas Starzl: As you know, we were interested in the possibility of aldosterone changes which we investigated with you 2 or 3 years ago. There seemed to be hyperaldosteronism for a period. However, in the long run no matter how extensive the resection, the patients became completely well. One of our patients, whose specimen is shown in figure 12 had a resection that approached 90% and probably is one of the most extreme subtotal resections that has ever been successfully done.[53] That patient developed ascites that lasted for several months. She lost all of her hair and her fingernails. These findings completely went away after 6 or 7 months even though liver regeneration, as judged by scan, was not complete. Since then, I have heard of another similar pateint in whom the syndrome of reversible ascites and alopecia developed. But, in the long run, if the patients survive operation, they can expect to become completely normal even though the mass of hepatic tissue is not completely restored.

Dr. Sunder Mehta: Is the angiogram diagnostic in differentiating hyperplasia from adenoma?

Dr. Thomas Starzl: No, there are no specific angiographic features that permit a differential diagnosis.

Dr. Fred Kern: In summary, today we have presented 2 patients who probably represent examples of complications of oral contraceptives, and have discussed briefly the current state of knowledge about three major clinical effects of estrogens upon the liver: cholestasis, cholesterol gallstones, and hepatic adenomas. The certainty of the latter association has been questioned. Some of the major effects of estrogens upon the hepatic cell are shown diagramatically in figure 13.

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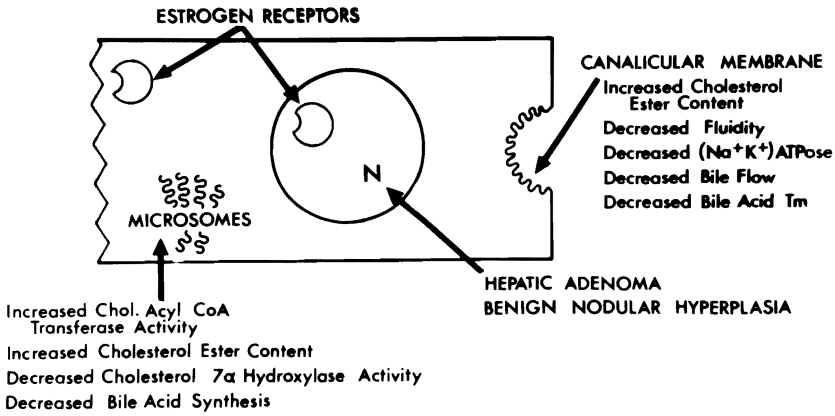

FIG. 13. Diagram of major effects of estrogens upon the liver cell, showing sites of action and proposed mechanisms of effects on the canalicular and microsomal membranes.

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