
Failure of Hepatic Adenomas (HCA) to Regress After Discontinuance of Oral Contraceptives

An Association with Focal Nodular Hyperplasia (FNH) and Uterine Leiomyoma

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Oral contraceptives have been implicated in the development of hepatic cellular adenomas (HCA) and associated in at least one report with focal nodular hyperplasia (FNH). Recurrence of lesions or progression while the patient is no longer receiving exogenous steroids is less well documented. Three cases are reported in which progression or recurrence of HCA after the discontinuance of steroids was documented. In addition, FNH and uterine leiomyomas with HCA were observed in all three cases. The mechanism of tumor formation secondary to the use of oral contraceptives remains undetermined. In two cases, liver tissues were tested for estrogen receptors; both were found to be negative. Although technique as well as the observed progression of these lesions or development of new lesions after the discontinuance of steroids may account for this negative finding, it suggests that induction of this process may be caused by means other than direct cellular stimulation by the exogenous hormones. Finally, these three cases call attention to a potential subgroup of patients having oral contraceptive-associated HCA who may have progression of their liver tumors when no longer receiving steroids and who require an aggressive treatment program and noninvasive follow-up examinations.

THAT THERE IS AN association between the use of oral contraceptives and the development of hepatic cell adenomas (HCA) was initially suggested in 1973 by Baum et al.,¹ and has been supported by numerous reports since that time.²⁻¹² In some early reports, other liver tumors, including focal nodular hyperplasia (FNH) and hepatocellular carcinoma, were also believed to be related to oral contraceptive use. However, most investigators now consider HCA the only tumor clearly associated with oral contraceptive use. Furthermore, during the past ten years it has been shown that discontinuation of hormonal therapy usually results in regression of HCA that are biopsied but not excised. It is generally accepted that small or

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inaccessible, asymptomatic HCA can be safely observed after cessation of oral contraceptives, because involution of the adenoma is to be expected. The only reported exception is that which Mariani et al. reported, in which there was well documented progressive enlargement of an HCA, despite cessation of hormone use.¹³

The purpose of this paper is to report three cases in which HCA progressed after patients were no longer receiving steroids. These cases were associated with life-threatening complications. In two of our three patients, HCA were present concomitantly with focal nodular hyperplasia. Uterine leiomyomata were present in all three cases. In addition, during follow-up we were able to document continued enlargement of a pre-existing HCA that, in one patient, could not be removed during a previous operation, and the appearance of a new HCA in the apparently normal unresected liver of a second patient.

Case Reports

Case 1

A 34-year-old black female nurse, gravida 0, had used oral contraceptives for a 2-year period, but had taken none for the 7 years preceding hospitalization. She was in excellent health until 6 months before hospitalization, when she was admitted for a short period of observation after a minor auto accident. Her seat-restraint had prevented any major injuries. Three months later she was involved in another minor motor vehicle accident. Again she was admitted for 24 hours of observation. About 10 days after this accident, she began to complain of right upper quadrant abdominal pain. Her physical examination was normal except for the finding of a right upper quadrant mass that was mildly tender to palpation. A radionuclide biliary scan (HIDA) revealed a large filling defect in the right hepatic lobe and a normally functioning gall bladder. Angiography revealed a large, relatively avas-

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cular liver lesion, in addition to several smaller blushing areas in the surrounding right lobe (Fig. 1). Preoperative laboratory studies were unremarkable. A diagnosis of HCA with concomitant FNH was made on the basis of the angiographic findings. It was considered likely that either hemorrhage or necrosis of the HCA caused her acute symptoms.

During the operation, a 10 cm lesion was palpable in the inferior aspect of the anterior segment of the right hepatic lobe. Several 2 cm diameter nodular lesions were also present in the right lobe. A massive pedunculated uterine leiomyoma and several smaller leiomyomata were discovered during exploratory surgery. A wedge excisional biopsy of one of the hepatic nodular lesions was interpreted as FNH by frozen section. Together with a margin of normal liver tissue, the larger lesion was totally removed by wedge resection. Permanent pathologic interpretation confirmed that the small nodule was FNH and the larger lesion was HCA (Figs 2A and B).

Gross sectioning of the HCA revealed a large cavity filled with old clot from intratumor hemorrhage (Fig. 3).

After surgery, the patient did well and was discharged on the 6th postoperative day, having normal liver function tests and tolerating a normal diet.

The patient returned to the care of her physician. Follow-up serial imaging studies were recommended but not obtained. The patient was not seen in our clinic again until 3 years later, when she presented with a complaint of right upper quadrant pain. A new tumor mass, 8 cm in diameter, was discovered in the left medial segment by imaging studies. Hemorrhage within the mass was noted by magnetic resonance imaging (MRI) (Fig. 4A), but was difficult to discern through computerized tomogram (CT) with contrast (Fig. 4B). The patient was returned to the operating room, where complete excision of the involved lesion was performed. Her postoperative course was uneventful and she was discharged, having normal liver function tests and receiving a normal diet. She has done well during 6 months of follow-up.

Case 2

A 36-year-old white female, gravida 3, para 3, had used oral contraceptives for a 3-year period, but had not used any for the 6 years preceding hospitalization. Two weeks before admission, she had undergone a transabdominal hysterectomy for large leiomyomata. During a routine exploratory, a large liver mass was palpated. After surgery, a selective hepatic angiogram showed a large vascular tumor occupying most of the right lobe of the liver (Fig. 5). A diagnosis of HCA was considered most likely. The patient was transferred to our hospital for further care. All other preoperative tests were unremarkable. During exploratory surgery, a 12 cm smooth ovoid mass was discovered in the right lobe of the liver, involving both anterior and posterior segments. Several areas consistent with FNH were identified adjacent to the mass. A right hepatic lobectomy was performed without difficulty. Microscopy confirmed the clinical impression that the smaller lesions were FNH and that the large mass was an HCA. Estrogen and progesterone receptor assays were negative. Her postoperative course was uneventful, and she was released on the 8th postoperative day, having normal liver function tests and tolerating a normal diet. She has done well during 4 years of follow-up.

Case 3

A 37-year-old white female, gravida 2, para 1, used oral contraceptives for 2 years. She had not used oral contraceptives for 10 years before hospitalization. Six years before admission, she had undergone an emergent left lateral segmentectomy after rupture of an HCA and massive intraperitoneal hemorrhage. She underwent serial radionuclide liver-spleen scans and ultrasonography at 6–12-month intervals following that operation. All examinations were reportedly normal until an examination 2 weeks before admission. At that time, she was

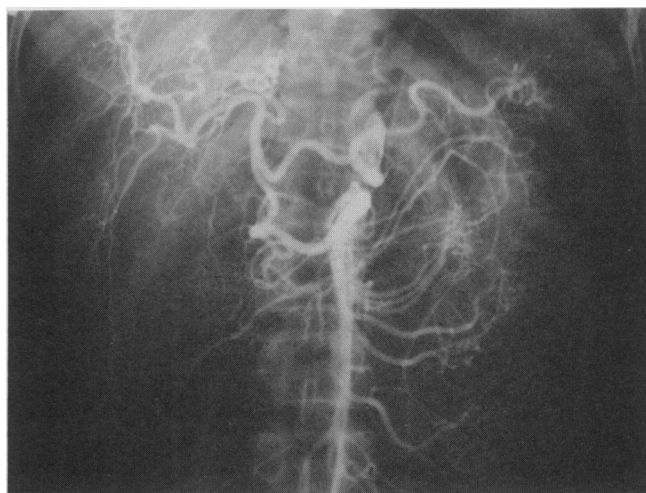


FIG. 1. Selective angiogram from the patient of Case 1, demonstrating a large, relatively avascular lesion of the right lobe of the liver that was found to be a hepatic adenoma at the time of operation.

found to have several new large sonolucent areas in the liver. She underwent abdominal CT and selective hepatic angiography, which more clearly defined these lesions (Fig. 6). A diagnosis of recurrent HCA was made, and she was transferred to our institution for further care. Her medications on admission were 40 mg of Corgard™ (Squibb, Princeton, NJ) daily and Dyazide™ (SK&F, Philadelphia, PA) one tablet daily for essential hypertension. Other significant history included a dilatation and curettage for fibroids 2 weeks before admission, and 9 years before admission an ectopic pregnancy, for which she underwent bilateral tubal ligations. Her preoperative workup was unremarkable.

During the operation, two large masses were evident—one in the medial segment of the left lobe, and one in the anterior inferior portion of the right hepatic lobe. A third lesion evident on CT in the posterior right lobe could not be palpated or visualized. Except for the presence of several small uterine leiomyomas, the remaining exploratory was normal. The two accessible lesions were excised with surrounding rims of normal liver.

Microscopy showed these lesions to be HCA. No further lesions were noted in the specimens. Estrogen and progesterone assays were negative. The postoperative course was unremarkable and the patient was released from the hospital, having normal liver function tests and tolerating a normal diet. She has done well during the 3 years of follow-up.

Discussion

The association of oral contraceptive use and the development of benign liver tumors has been well established in the medical, radiological, and surgical literature. Since the time that the first six cases were reported by Baum et al. in 1973,¹ the volume of documented cases has grown to include more than 500. Excellent reviews have been published in recent years by Sherlock, Terblanche, and Kerlin et al.^{8,10,14} Despite the reservations of some, the weight of evidence supports the original hypotheses that oral contraceptive use is associated with the development of benign liver tumors.

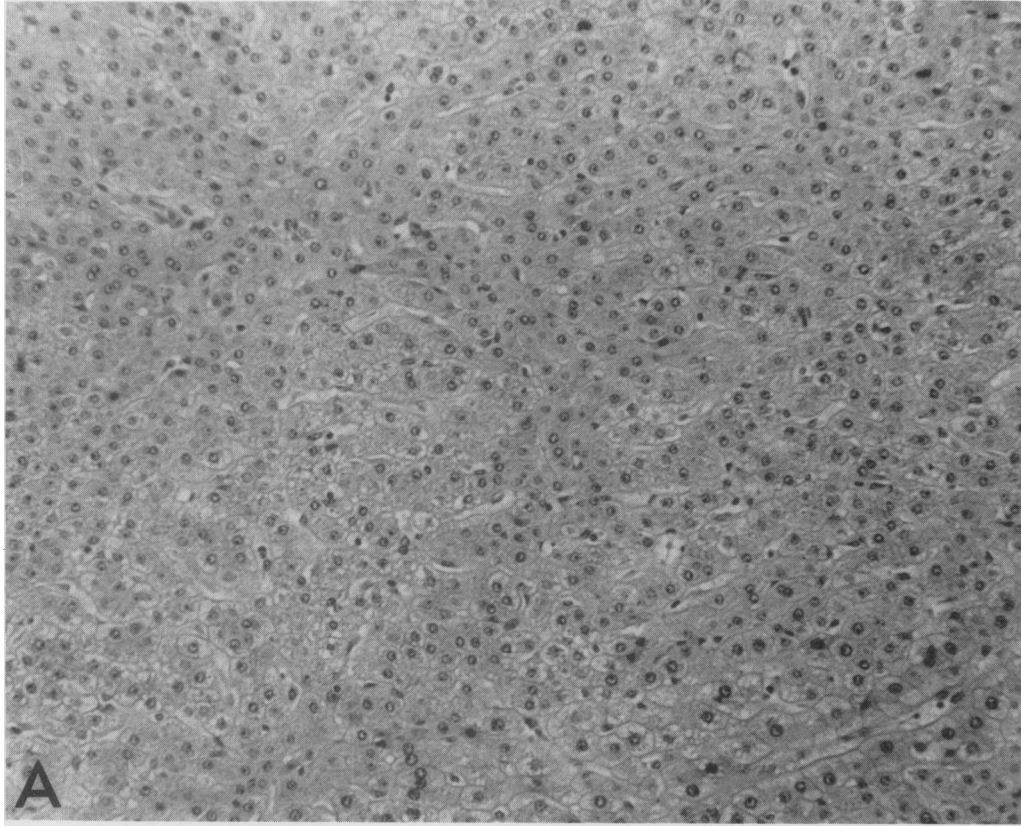


FIG. 2A. Photomicrograph of FNH from the patient of Case 1.

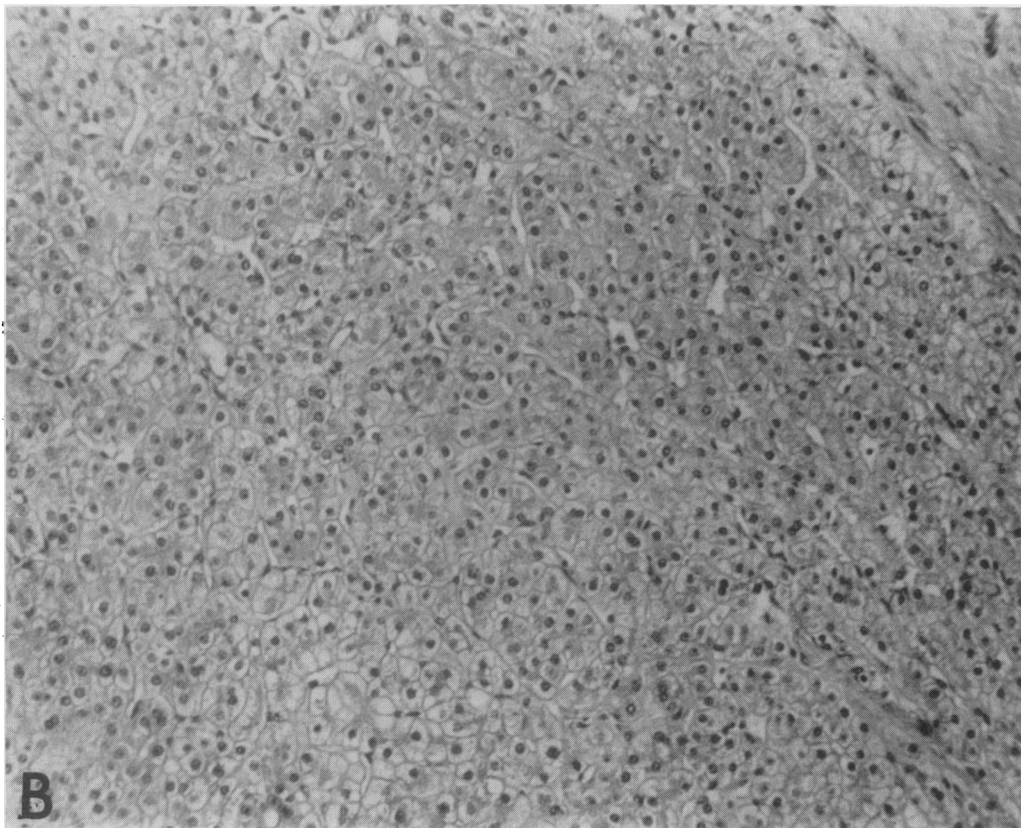
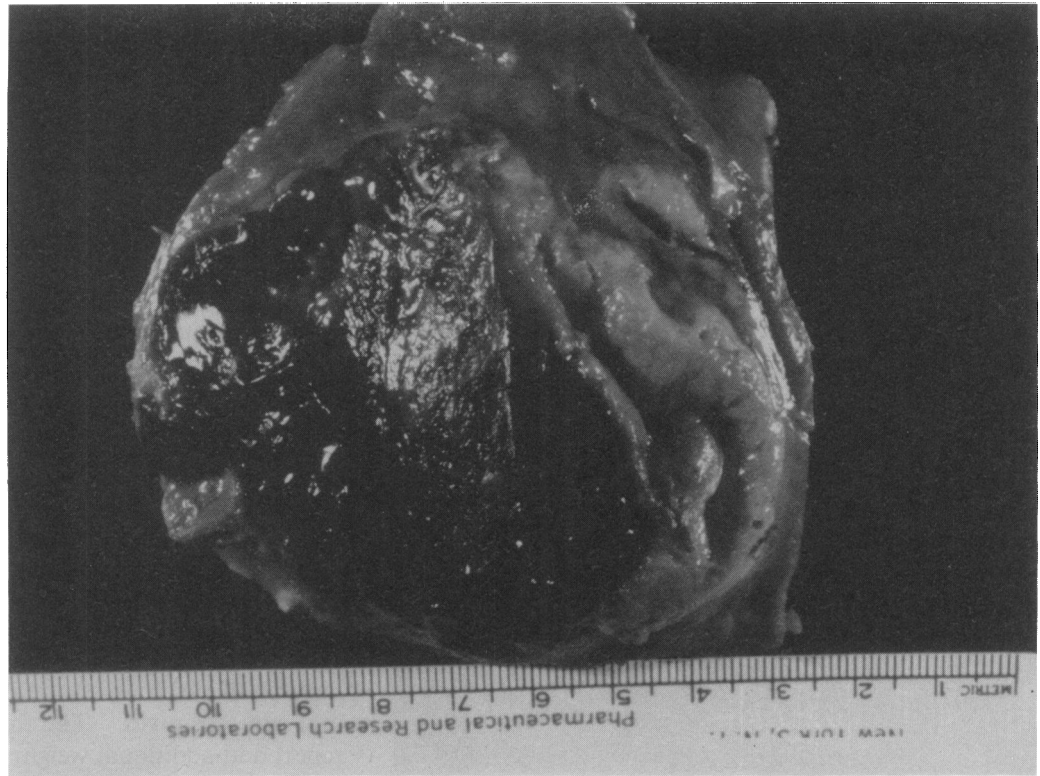


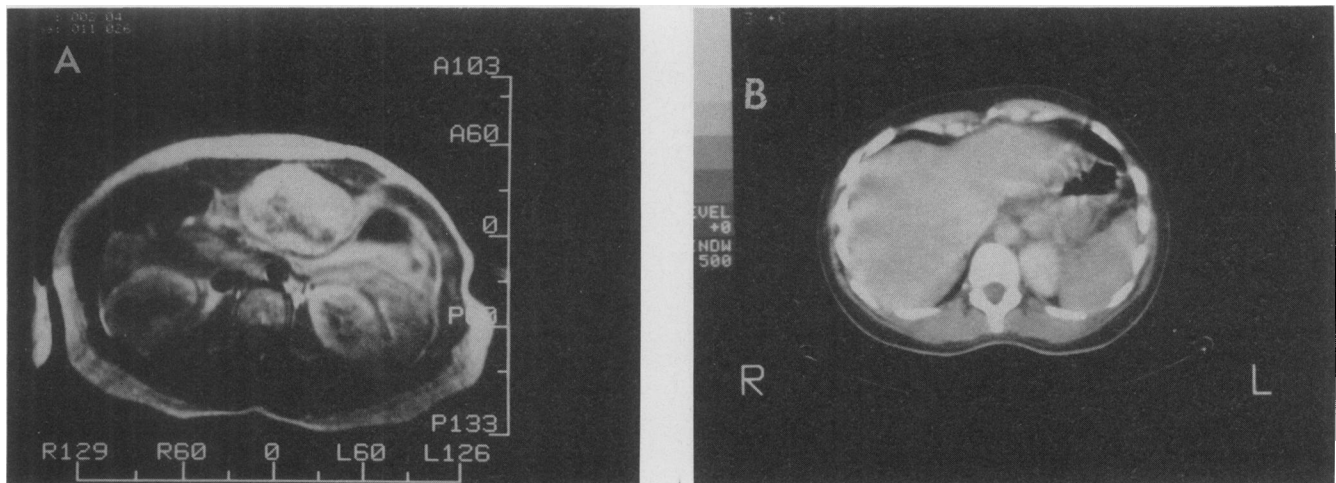
FIG. 2B. Photomicrograph of HCA from the patient of Case 1.

FIG. 3. Gross specimen of hemorrhagic lesion of the liver removed by wedge resection with a rim of normal liver from the patient of Case 1.



These lesions are of several types. The vast majority are HCA. Microscopically, these tumors consist of apparently normal liver cells, without the presence of bile ducts or central veins. The tumor is usually solitary, although multiple lesions have been reported. FNH is found less frequently. Characteristically, FNH demonstrates central scar formation with proliferating bile ducts, from which fibrous septa radiate. In some case reports, differentiating HCA from FNH has been confusing. It is currently believed that FNH in oral contra-

ceptive users may be a coincidental finding, and that tumors associated with symptoms of rapid growth or hemorrhage are nearly always HCA. However, exceptions have been reported in which oral contraceptives and pregnancy have been shown to influence FNH.¹⁵ Therefore, the effect of the hormonal milieu on FNH has not been resolved. Peliosis or focal vascular sinusoidal dilatation without an endothelial lining may be found either alone or in association with either HCA or FNH. The major controversies over these lesions no



FIGS. 4A and B. (A) Nuclear magnetic resonance scan of the upper abdomen obtained from the patient of Case 2, demonstrating a large mass in the left medial segment the liver. (B) Computerized tomogram, with contrast, of the same area as that imaged in Figure 4A. Note the relative insensitivity of this technique in defining the lesion that was proven to be a recurrent HCA at operation.

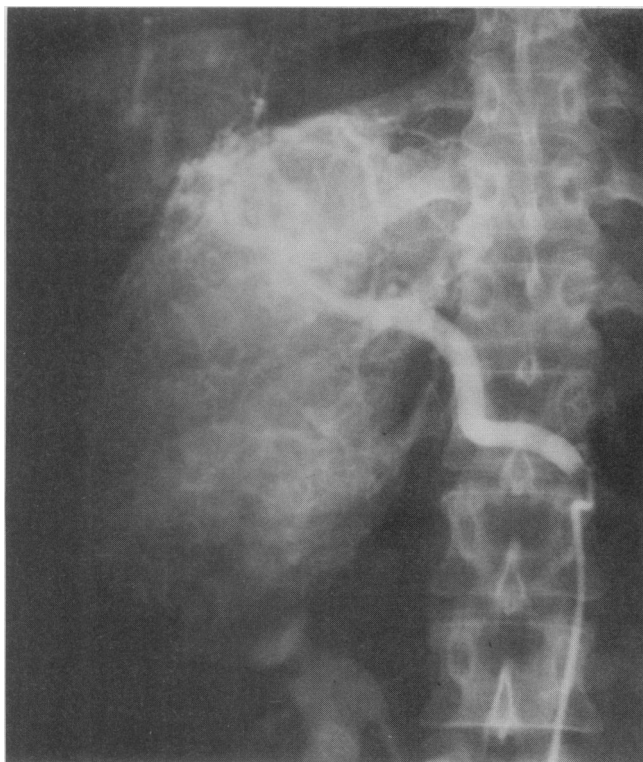


FIG. 5. Selective angiogram of right lobe of the liver from the patient of Case 3, demonstrating a large vascular tumor. At the time of operation, this proved to be an HCA.

longer center on their association with oral contraceptives, but rather on whether or not such lesions undergo malignant change, and on specifying the most appropriate treatment for these lesions, particularly when they

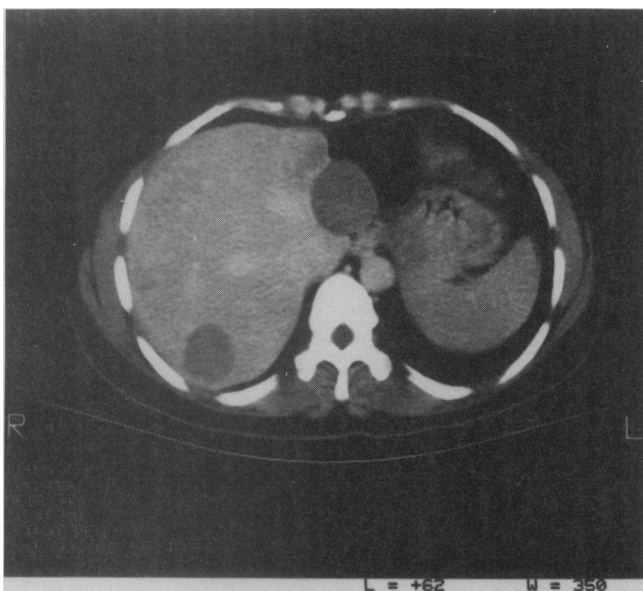


FIG. 6. Computerized tomogram from the patient of Case 3, demonstrating two recurrent lesions of the liver. At the time of operation, these proved to be HCA.

are asymptomatic. The weight of current evidence indicates that malignant change in an HCA rarely if ever occurs, except in patients having type Ia glycogen storage disease.^{14,16,17}

A real and pressing concern in regard to HCA is their potential for rupture and catastrophic hemorrhage. It has been demonstrated that withdrawal from oral contraceptives results in regression of most HCA. Emphasis has therefore been placed on the role of conservatism in their management. Sherlock strongly advocates a conservative approach to these lesions, suggesting that only tumors causing symptoms or associated with complications should be removed. She recommends that lesions be left *in situ*, that sex hormones be discontinued, and that the tumors be observed for regression every 6 months, using ultrasonography and/or liver scan.¹⁰

Evidence of tumor regression has substantiated the opinion that estrogen or progesterone stimulation is an important pathogenic mechanism for their development. Mariani et al. reported a single case in which an HCA was noted to increase in size, as determined by noninvasive techniques, despite the discontinuation of oral contraceptives.¹³ The three cases presented in this report add additional weight to the evidence that some of these tumors may continue to enlarge and become symptomatic without exogenous hormonal stimulation or pregnancy. In all three of our cases, oral contraceptives had been discontinued for more than 5 years before the discovery or reappearance of these lesions, and in two cases, symptomatic "new" lesions were documented years after use of hormones had been discontinued.

Significant bleeding can result from these lesions after relatively minor trauma, or can occur spontaneously as they enlarge. Since elective tumor resection is accompanied by a low morbidity, we support the position of Terblanche et al. that large (>5 cm) lesions should be removed at the time of exploratory surgery.⁸ FNH, which is unlikely to cause a bleeding problem, and multiple or solitary HCA, which cannot be removed without a complete lobectomy, are best treated initially by conservative management after their histological diagnosis has been verified. Until involution is documented, the use of oral contraceptives should be prohibited, and serial noninvasive imaging examinations should be performed every 3–6 months. Although most small HCAs do regress, these cases demonstrate that a subset of patients appear to be at continuous risk after the development of an HCA. Furthermore, patients with a history of these tumors and who wish to become pregnant should be serially studied by noninvasive means and should be counseled appropriately concerning their added risk of hemorrhaging spontaneously during gestation.

The patients presented in this paper represent a subset of previously unrecognized patients with oral contraceptive, related HCA. In the cases of these patients, lesions continued to enlarge, or at least failed to regress, despite the discontinuance of all steroid-related compounds. In two of the three patients, new lesions developed. As these lesions have clearly shown their potential for symptomatic recurrence, frequent follow-up examinations using ultrasonographic imaging and early surgical intervention are preferable to conservative therapy. We believe that tumors larger than 5 cm in diameter that fail to involute within 6 months should be electively excised. Two of our cases were found to have concurrent FNH and HCA. These two lesions are rarely demonstrated in the same patient. In addition, all three of these patients were found to have uterine leiomyomas.

The significance of the concurrence of uterine leiomyomas with liver lesions is unclear. The influence that estrogens have on these uterine lesions is well known, and the possibility that their growth represents an imbalance in the estrogen-progesterone ratio is suggested by the observation that these lesions tend to grow when estrogen is unopposed by progesterone. Liver parenchyma is known to contain estrogen receptors and, therefore, it is tempting to postulate similar mechanisms of tumor induction by oral contraceptives for both the liver and the uterus. In a recent article, Porter et al. reported that biopsies of HCA and FNH contained cytosolic and nuclear estrogen receptors.¹⁸ The nuclear estrogen receptor levels were significantly elevated in HCA and FNH as compared to normal tissues. However, in one case of HCA in which the patient was taking tamoxifen, nuclear and cytosolic estrogen receptor levels were either absent or significantly lower than in normal tissues. We were able to test for estrogen receptors in the HCA tissues from two of our patients. These assays were negative in both cases. This may have been due to differences in technique between the two studies. Thus, the evidence that there is a direct stimulatory role for estrogen in the generation of these lesions remains in question. Mechanisms for induction of these lesions by estrogen other than direct cellular stimulation exist as evidenced by Fischer et al.¹⁹ Using immunohistological techniques, they noted that liver tissues surrounding areas of FNH in patients with a history of long-term oral contraceptive use demonstrated altered enzyme patterns similar to those observed in animal models during experimental hepatic carcinogenesis.

These cases demonstrate the absolute necessity for regular long-term monitoring of patients having HCA. In addition, we conclude that an early and aggressive course is warranted in the treatment of patients with known progression of the disease or failure of an HCA to

involute within 6 months after discontinuance of exogenous hormones.

Further, our observation of fibroid tumors coexisting in all three of these young patients points out the necessity of a thorough abdominal exploratory in any patient with a history of oral contraceptive use undergoing hysterectomy for fibroids. It remains to be determined whether the association of fibroids with oral contraceptive HCA indicates a subgroup of patients who are likely to have progression of liver tumors even after their exogenous hormones are discontinued.

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