Influences of Hormones in Tumor Development

Volume II

Editors

John A. Kellen, M.D., Ph.D.,

Russell Hilf, Ph.D.

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John A. Kellen, M.D., Ph.D.,

Associate Professor
Department of Clinical Biochemistry
Sunnybrook Medical Centre
University of Toronto
Toronto, Ontario, Canada

Russell Hilf, Ph.D.

Professor of Biochemistry
University of Rochester
School of Medicine and Dentistry
Rochester, New York

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PREFACE

The increasing awareness in recent years that our environment directly or indirectly influences carcinogenesis has focused much of our attention on external factors. What is being held as general deterioration in the quality of the environment has been widely reported on and has become an important area of social and scientific concern. This has come to outweigh our concern for the part played by the internal milieu and by genetic susceptibility. No critical assessment of the complex interplay of modifiers that finally lead to malignant growth should ignore this triad. There is no doubt that in some cancers, the influence of one or more factors seem of overwhelming importance. However, it appears reasonable that, whatever theory of primary cancerogenesis* one may adhere to, internal modulation of the exposed tissue is a necessary prerequisite for tumor induction and growth.

Hormones have traditionally been assigned an important role as modifiers of the neoplastic process. Their key role in metabolism makes them a logical target for speculation of this kind. The exquisite balance between the hormones in response to physiological needs, the minute amounts of active substances acting at the molecular level, and the continuing elucidation of the amplifying systems which translate their messages, all offer potential controls where the observed changes might be affected. Hormones are not necessarily components of mitotic mechanisms; cells can divide in their absence, but the overall regulation of cell division seems to be under their control. Hormones are also capable of affecting the genetic regulatory system by modifying gene expression.

It is accepted that hormones modify cancer risk, the response of the body to carcinogens and the biological behavior of established tumors. Some hormones seem to produce tumors directly, albeit at heroic levels. Experiments involving the removal of glands that secrete substances which stimulate or support tumor growth have destroyed the idea that all cancers were independent growths. At least some tumors, like many endocrine target tissues, can be shown to be dependent on normal control mechanisms. Our knowledge on therapeutic effects of hormones has been beneficial to innumerable patients.

Tumors of endocrine organs and of organs controlled by hormones cause some 90,000 deaths out of an estimated total number of 350,000 cancer deaths in the U.S. per year. Hormone-induced tumors, ectopic hormone production, and efforts to influence the natural history of tumors by administration of hormones in experimental animals represent a considerable share of basic research. The last decade has brought about a major qualitative step in our armamentarium with the discovery of hormone receptors which already has an increasing impact on clinical thinking.

The successful attrition of billions of malignant cells in a clinically apparent tumor — a cancer "cure" — evokes much scepticism. On the other hand, step-by-step modulation of such cells towards redifferentiation by endocrine therapy does not seem to be impossible to achieve.

We have tried to present an assessment of these uncertainties and challenges in basic research with clinical implications. We have divided the information on current views and results into sections by hormones. In these, the much appreciated work of our coauthors may be seen. It is next to impossible to cover this dynamic and wide-ranging topic comprehensively, but we hope that an updated review of relevant experimental and clinical research will contribute to the development of this promising field of enquiry.

* For a note on the distinction between cancerogens and carcinogens, the reader is referred to *Nature* (London), 267, 306, May 26, 1977.

The relationship of hormones to neoplasia is complex and multifaceted; it is conceivable that better understanding and manipulation of this relationship will pave the way for more rational and effective treatment of many cancers.

J. A. Kellen
R. Hilf

THE EDITORS

Dr. John A. Kellen is Associate Professor and Staff Physician in the Department of Clinical Biochemistry at the Sunnybrook Medical Centre, a teaching hospital of the University of Toronto.

His primary interest is in immunology and biochemical markers in cancer; he has over 170 scientific papers and three monographies to his credit. Dr. Kellen is also Medical Editor of *Modern Medicine of Canada*. The selection of Chapters and Authors for this book were his responsibility.

Dr. Russell Hilf is Professor of Biochemistry and of Oncology, University of Rochester School of Medicine and Dentistry, Rochester, New York. His current research interests include the study of hormone action on breast cancer in humans and rodents and the investigation of methods to predict response to therapy. Dr. Hilf has published more than 150 research papers, has served as an Associate Editor for the journal *Cancer Research* and is currently on the Advisory Board for *Cancer Biochemistry Biophysics*. Since 1976, he has been a member of the Breast Cancer Task Force Committee, National Cancer Institute, National Institutes of Health, Bethesda, Maryland.

CONTRIBUTORS

K. M. Anderson, M.D., Ph.D.
Associate Professor of Biochemistry
Rush University
Chicago, Illinois

Jacques Asselin, Ph.D.
Assistant Professor
Laval University
Quebec, Canada

William T. Cave, M.D.
Assistant Professor of Medicine
University of Rochester School of Medicine
Rochester, New York

Yoon Sang Cho-Chung, M.D., Ph.D.
Research Biochemist
National Cancer Institute
National Institutes of Health
Bethesda, Maryland

Victor A. Drill, M.D., Ph.D.
Professor of Pharmacology
University of Illinois College of Medicine
Chicago, Illinois

Bernard A. Eskin, M.D.
Director of Reproductive Endocrinology and
Associate Professor of Obstetrics and Gynecology
Medical College of Pennsylvania
Chief, Gynecologic Endocrinology Section, Division of Obstetrics and Gynecology
Albert Einstein Medical Center
Philadelphia, Pennsylvania

Edward H. Fowler, D.V.M., Ph.D.
Manager of Pathology and Laboratory Animal Resources
Department of Pathology
Carnegie-Mellon Institute of Research
Pittsburgh, Pennsylvania

Joan T. Harmon, Ph.D.
Postdoctoral Fellow
Diabetes Branch, NIAMDD
National Institutes of Health
Bethesda, Maryland

Russell Hilf, Ph.D.
Professor of Biochemistry
University of Rochester
School of Medicine and Dentistry
Rochester, New York

Vincent P. Hollander, M.D., Ph.D.
Professor of Medicine and Director
Research Institute, Hospital for Joint Diseases and Medical Center
New York, New York

John A. Kellen, M.D., Ph.D.
Associate Professor
Department of Clinical Biochemistry
Sunnybrook Medical Centre
University of Toronto
Toronto, Ontario, Canada

Paul A. Kelly, Ph.D.
Senior Member
MRC Group in Molecular Endocrinology and Assistant Professor
Department of Physiology
Laval University
Quebec, Canada

N. A. Kerenyi, M.D., F.R.C. (Pathol.)
Associate Professor of Pathology
University of Toronto
Toronto, Ontario, Canada

Fernand Labrie, M.D., Ph.D. F.R.C.P.(C)
Professor and Director
MRC Group in Molecular Endocrinology
Laval University,
Quebec, Canada

Robert M. MacLeod, M.D., Ph.D.
Professor of Medicine
University of Virginia School of Medicine
Charlottesville, Virginia

J. W. Meakin, M.D., C.M., F.R.C.P.(C)
Executive Director
The Ontario Cancer Treatment and Research Foundation
Toronto, Ontario, Canada

B. G. Mobbs, Ph.D
Clinical Research Associate
Ontario Cancer Treatment Research Foundation
Assistant Professor of Surgery
University of Toronto
Toronto, Ontario, Canada

Arthur H. Rossof, M.D.
Assistant Professor of Medicine
Rush Medical College
Chicago, Illinois

N. A. Samaan, M.D., Ph.D., F.A.C.P., F.R.C.P.
Professor of Medicine and Physiology and Chief, Section of Endocrinology
The University of Texas System Cancer Center
M. D. Anderson Hospital
Professor of Medicine
The University of Texas Medical School
Houston, Texas

Samir M. Shafie, Ph.D.
Visiting Scientist
Laboratory of Pathophysiology
National Cancer Institute
National Institutes of Health
Bethesda, Maryland

John Stevens, M.D.
Head
Leukemia Section
Research Institute, Hospital for Joint Diseases and Medical Center
New York, New York

Yee-Wan Stevens, M.S.
Research Assistant
Research Institute, Hospital for Joint Diseases and Medical Center
New York, New York

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Chapter 1

THE INFLUENCE OF ANDROGENS ON TUMOR DEVELOPMENT

K. M. Anderson and A. H. Rossof

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I. INTRODUCTION

Before considering the influence of testosterone and its congeners on the development and subsequent growth of different cancers, ideally the structures, sites of synthesis, and some cellular and subcellular biochemical effects of male sex hormones should be discussed. In lieu of this, the reader is referred to some of the excellent

recent (post-1972) reviews concerning the physiology and biochemistry of androgens.[1-14] Those whose major interests are in other fields will find these subjects examined in great detail with copious documentation; the specialist in this field is already aware of the extensive information they contain.

For the authors purposes, androgens encompass the natural and synthetic derivatives of the C19 steroid nucleus (5 α-androstane) able to maintain the secondary sexual characteristics of experimental animals. Synthetic compounds include alkylated and nonalkylated androgens and derivatives of 19-nortestosterone.[14]

The nature of the biochemical events that follow administration of androgens can vary from the induction of cell division with the wide range of new RNA transcripts that this implies, to amplification of ongoing metabolic processes during cell growth that is independent of cell division,[15] to a much more limited stimulation of specific enzymatic activity, such as β-glucuronidase in the mouse kidney by 5α-androstanediols.[16] Many, but not all (e.g., induction of β-glucuronidase) of these events seem to require qualitative or quantitative alterations in transcription of RNA. Androgens appear to function as switches to select specific developmental pathways, to activate events leading to cell division, or to amplify ongoing differentiated metabolic processes. The relationships between these different functions are not established. Expression of major developmental pathways involves replication of specific cells leading to particular intrinsically programmed biochemical events.

Any speculations about how androgen receptors (see Mobbs, in Volume I, Chapter 2) alter transcription must incorporate recent information about the organization of chromatin into subunits or nucleosomes. According to some reports, all genomic sequences are included in the repeat structure, the particles are randomly distributed, and include both active and inactive template. Other workers believe that template active regions of chromatin consist of more open and extended regions of DNA, devoid of histone-rich, RNA-free nucleoprotein complexes sedimenting at 11 to 13S. Participation of higher order folding of chromatin and of acetylation and phosphorylation of histone and nonhistone proteins in the control of gene expression are subjects of active study, although most of this work has not been performed in androgen-sensitive tissues.

Rapid in vivo and in vitro changes in phosphorylation of nuclear acidic proteins from the ventral prostate follow the administration of testosterone,[17] and the central role of acidic nuclear proteins in mandating the response to androgens is indicated.[18] The number of nuclear binding sites for androgen receptors, the nature of the acceptor material (whether protein, DNA, or their combination), the effect of added cytosol receptor on the activity of purified RNA polymerases and the template activity of prostate chromatin,[19] the function of the DNA unwinding protein,[20] effects of androgens on protein synthesis independent of new RNA synthesis,[21] and interactions between cytosol and nuclear protein kinases, cyclic nucleotides and enzyme activity[22] all represent active areas of study. Any of them may prove to be important for understanding how androgens can modify tumor growth and development. Progesterone cytosol receptor is believed to include two subunits; the B subunit binds specifically to acidic chromosomal proteins (AP_3) while the A component associates in a nonspecific manner with DNA.[23] The extent to which androgens or other steroid hormone receptors mimic this pattern is not yet established.

II. GENETIC AND EPIGENETIC CHANGES IN CARCINOGENESIS: POINTS OF INTERACTION WITH ANDROGENS

It is widely agreed that steroid hormones are not proximate carcinogens in the manner of carcinogenic hydrocarbons and other active agents.[24-26] Their tumor-promoting

activity is believed related to imbalance of normal physiological functions. Thus, increased cancer incidence due to androgens (and possibly some other steroid hormones) is not thought to be due to direct but rather indirect effects on target cells that potentiate the actions of other proximate agents.

The Ames mutagenicity test provides evidence of mutagenicity in a bacterial test system and of the presumption of carcinogenicity in metazoans.[27] With few exceptions, agents that are carcinogenic in man or animals are mutagenic in that system. For example, diethylstilbestrol is weakly mutagenic and its administration to several animal species is associated with development of cancer, while carcinoma of the vagina develops in a small percentage of young women whose mothers received the drug during early pregnancy for threatened abortion.[28] The authors have been unable to document the possible mutagenicity of androgens examined by the Ames test, but this information should provide direct evidence concerning this point. If androgens are mutagenic in this system, presumably they will be able to function as proximate carcinogens. However, inability to transform organ or tissue culture cells grown in their presence suggests that they may not function in this manner (see Section III.D). Steroids can physically associate with histones and DNA in vivo and in vitro, which could be a prerequisite for altering the function of the DNA template. Irreversible binding of norethisterone epoxide to proteins with SH groups but not to DNA and RNA has been observed, which required incubation with a superoxide generating system provided by hepatic microsomes.[29] Such reactive intermediates might bind to nuclear proteins and modify their function.

The classical two-step model of carcinogenesis in the skin, including an initiating event due to a proximate carcinogen and subsequent effects of promotion on the development of skin cancers, is well known.[30] Knudson proposed a two-mutation model of retinoblastoma involving a prezygotic (germ cell) mutation plus a postzygotic (somatic cell) mutation. Comings suggested that the double mutation released a tissue specific transforming gene.[31] Cells are thought to possess multiple structural genes capable of coding for transforming factors that release cells from normal constraints on their growth. Regulatory genes, presumably paired, would suppress these tissue-specific transforming genes.

The hypothesis that cancer arises as a consequence of two or more mutations in a single cell was examined by Nordling who suggested that the age-specific incidence, $I = kt^{r-1}$, where t reflects age and r the number of mutations.[32] Overall cancer mortality in many countries increases with age as the sixth power of time, implying that r was equal to seven. Armitage and Doll[33] concluded that the age-incidence of cancer of the stomach, colon, rectum, and pancreas was consistent with this, while cancers of the lung, bladder, ovary, endometrium, cervix, breast, and prostate were not. This latter group of cancers might be subject to varying initiating and promoting influences, such as age-dependent effects of endocrine changes, over the lifetime of the individual. When this formulation was applied to latent and clinical prostatic cancer and plotted on a double logarithmic scale, a linear relationship between frequency and age was obtained.[34] The slope of the line was greater for clinical cancers, corresponding to the seventh power of age, suggesting that latent cancer results from a smaller number of "hits" than clinical prostatic cancer. Increasing frequency of a cancer with age might be due to continued or increased exposure to a carcinogen or to some direct or indirect but unknown consequence of aging (e.g., reduced ability to repair damaged DNA, etc.).

A requirement for more than one necessary event (multiple hit theory[35]) in the development of many clinical cancers clarifies the phenomena of latency, penetrance, and pleiotropism (occurrence of cancer in more than one organ) and is compatible with the concept of tumor progression embodied by Foulds six general principles of tumor progression.[36]

However, it is not settled that the events leading to neoplastic change need to be mutations in the sense of defects in DNA (point mutations, deletion of base pairs leading to frame shifts, etc.). Clonal development of cancer from a single cell might arise from disordered functional development due to epigenetic causes.[37] Proponents of this idea suggest that critical events in carcinogenesis may involve abnormal cytoplasmic control of nuclear gene function and need not primarily depend upon altered DNA for its expression. It is argued that the basic cellular mechanisms that underlie normal differentiation and cancer are fundamentally similar, but in the latter process, expression of the cells developmental pattern is abnormal. The totipotency and normal differentiation of single teratocarcinoma cells injected into mouse blastocysts is consistent with the view that teratocarcinogenesis involved changes in gene function rather than gene structure, which was restored to normal by an appropriate environment.[38]

From one point of view, cancers, whether of genetic or epigenetic origin, can be viewed as examples of blocked cellular differentiation, with the retention of a matrix of biochemical reactions inappropriate for a differentiated cell from the tissue of origin.[39] If a program for normal development of a cell is represented as a series of multiple, interrelated, branching Markov chains with a large number of links,[40] interdiction of particular events required for normal growth and differentiation by epigenetic rather than genetic means should result in phenotypically comparable developmental defects. The problem of imagining ways that steroid hormones might directly or indirectly induce crucial epigenetic changes leading to cellular autonomy is different from suggesting mechanisms that require direct modification of cellular DNA.

Generally, experimental hormone-induced carcinogenesis has been studied by repeated administration of excess hormone to attempt overstimulation of the target organ or by creating hormonal imbalance (e.g., suppress negative feedback due to estrogen by implantation of ovaries in the spleen, etc.). Berenblum has classified seven types of cocarcinogenesis.[30] If it is unlikely that androgens serve as direct (proximate) carcinogens and as there is presently no evidence that they serve as additive, synergistic, or incomplete cocarcinogenic agents as defined by Berenblum, their participation in one of the other categories of cocarcinogenic events is possible. Permissive influences affect rates of absorbtion, metabolism, or detoxification of the active agent; preparative action renders the target organ more susceptible to a carcinogen; conditional influences modify the continued growth of a transformed cell; and lastly, enhancement of a putative effect of a virus on the target cell could occur.

Although they are not mutually exclusive, participation of androgens in mechanisms two through six can be considered (Table 1). It is also clear that alternative formulations of this problem are possible.

III. ANDROGENS AS CARCINOGENS OR COCARCINOGENS

A. Cancer Associated with Administration or Secretion of Androgens in Man

1. Clinical Observations

A variety of C_{17}-substituted androgenic-anabolic steroids have been associated with the development of hepatic neoplasms in humans (Table 2). The precise nature of these tumors varies considerably from case to case. Although frequently referred to as hepatocellular carcinomas or hepatomas, the behavior of many of these tumors bears little resemblance to typical human hepatomas.

The first case reported occurred in a 27-year-old male Caucasian with Fanconi's anemia (FA) who had been taking androgenic-anabolic steroid preparation for a number of years.[41] He died in hepatic failure and autopsy revealed "nodules...of hepatocellular carcinoma" (HCC) and postnecrotic cirrhosis. Since cirrhosis has long been recognized as a risk factor in the development of HCC, incrimination of these hor-

TABLE 1

Possible Mechanisms of Androgen-enhanced Carcinogenesis

I. Direct effects
   1. Binding to and modification of nuclear DNA or its associated proteins, or alteration of events in the cell cytoplasm which modify cell differentiation by epigenetic rather than genetic means
II. Indirect mechanisms
   2. Permissive effects, modifying the absorbtion, degradation of proximate carcinogens or their precursors
   3. Preparative actions, possibly by stimulating cell growth or cell division, rendering the target cell more responsive to carcinogenesis
   4. Enhance, by either deficient feedback inhibition or, less likely, by positive stimulation, the formation of hormonal or other growth-promoting agents which increase the development of cancer by chronic overstimulation of the target cells
   5. Conditional effects upon transformed cells, such as increasing the growth of a hormone-dependent tumor, modifying host immune resistence, etc.
   6. Conversion to another substance able to increase the incidence of tumors (e.g., androgens as precursors of estrogens)
III. Remote antecedent effects
   7. Permit the expression of cancer in an organ whose development required androgen-dependent embryonic induction with or without acquisition of phenotypic gender

TABLE 2

Androgens and Anabolic Steroids Administered to Patients Who Subsequently Developed Hepatic Tumors

Trivial name	Chemical designation
	17-Alkyl-substituted compounds
Methyl testosterone	17β-hydroxy-17-methyl-androst-4-ene-3-one
Testosterone enanthate	17β[(1-oxoheptyl)oxy]-androst-4-en-3-one
Stanozolol	17-methyl-2H-5α-androst-2-eno[3,2-c]pyrazol-17β-ol
Oxandrolone	17β-hydroxy-17-methyl-2-oxa-5α-androstan-3-one
Oxymetholone	17β-hydroxy-2(hydroxymethylene)-17-methyl-5α-androstan-3-one
Methandrostenolone	17β-hydroxy-17-methylandrosta-1,4-dien-3-one
	19-Nor compounds
Nandrolone decanoate	17β[(1-oxadecyl)oxy]-estr-4-en-3-one
Norethandrolone	17-hydroxy-19-norpregn-4-en-3-one

mones alone in the etiology or pathogenesis of HCC in this patient is in doubt. An additional patient with FA[42] developed a hepatoma on a background of posttransfusional macronodular cirrhosis and hemochromatosis, but she had never received androgenic hormone preparations.

The development of some form of hepatic neoplasia was reported in five other patients with FA who received androgenic-anabolic steroid preparations (AASP)[43-48] FA is an autosomal recessive disease characterized by microcephaly, growth retardation, skeletal malformation, brownish hyperpigmentation, occasional mental deficiency, and pancytopenia. There is also a proclivity for developing cancer both in the affected patient and his relatives.[49] The androgenic-anabolic steroid preparations are used to support the failing bone marrow. This disorder is also associated with chromosomal instability, and is manifested by enhanced transformation by SV40 of cultured fibroblasts[50] and defective DNA repair,[51] apparently the result of a deficient exonuclease.[52] Despite the reported association of HCC with ingestion of androgen-anabolic steroid

preparations, these extraordinary features of Fanconi's anemia somewhat weaken the argument that AASP constitutes a carcinogen or cocarcinogen for all humans.

A 21-year-old man with a syndrome described as a Fanconi variant, lacking the congenital anomalies, developed acute myelogenous leukemia. At postmortem examination, three 2.5-cm hepatic nodules were incidentally detected and were characterized as hepatomas.[53]

An additional six patients[44,54–57] with anemia (two with paroxysmal nocturnal hemoglobinuria[56,57] treated with AASP have developed hepatic tumors. In two patients, the lesions were multiple,[44] in three they were single,[55–57] and in one there was only clinical evidence of HCC without histopathologic confirmation.[54]

Hepatic tumors also developed in three patients without anemia but with endocrine disorders. A 68-year-old man who took methyltestosterone for 30 years for impotency developed a low-grade solitary HCC.[58] A 40-year-old man developed a solitary well-differentiated HCC after taking methyltestosterone for 8 years, along with thyroxin and cortisone for hypopituitarism.[56] After taking methyltestosterone and testosterone propionate for 8 years, a 33-year-old cryptorchid man developed a solitary, well-differentiated HCC.[56] A 27-year-old female transsexual taking 150 mg of methyltestosterone daily for 37 months presented with a painful right hypochondrial mass which upon surgery was found to be a liver adenoma.[59] Hearsay evidence is available that a body-builder who took anabolic steroids for a number of years developed Wilms tumor at the age of 38.[60] This is a common tumor of the mesonephric kidney in children but is extremely rare in adults, suggesting a possible association of this tumor with the use of AASP.

In many cases, the clinical behavior of these tumors is not consistent with that of the usual idiopathic HCC of human beings. In three cases,[44,56] there was clinical or roentgenographic evidence of tumor regression upon cessation of therapy with AASP. In other cases,[56] there were extended periods of life after tumor diagnosis. Although some patients died quickly[47,48] (more consistent with the usual clinical behavior of HCC), almost all of the tumors have been classified histologically as low grade, well differentiated,[43–45, 53,55, 56,58] or benign.[47,57,59]

Regression of these tumors, the chronicity of many cases, and the frequent bland histopathologic appearance all suggest that these neoplasms are not invariably malignant. The ultimate interpretation of the nature of these lesions is further hampered because many case reports are extremely brief and histopathologic material is reproduced in only six cases.[41,44,47,53] This is further complicated by some reviewers who do not accept the original histopathologic interpretations.[61,62]

In recent years, certain human neoplasms, including HCC, have been associated with the appearance in the serum of a protein marker, alpha fetoprotein (alpha FP). This marker was sought in 12 cases, but was positive in only 1[54] and this single case lacked histopathologic confirmation. Alpha FP was also increased in the one patient with FA who developed HCC without exposure to AASP.[42] The infrequent identification of this protein in this group of patients further defines the atypical character of this lesion.

Sweeney and Evans[47] reported one patient with FA and a benign hepatoma. Distant from the neoplastic lesion, they noted other hepatic changes, such as generalized hyperplasia and hepatocytic nodule formation. They observed two additional patients who had been taking oxymetholone and prednisone for 3 months each. Their hepatic histology also demonstrated nonneoplastic hepatocytic alterations such as mid-zone hyperplastic nodules and thickening of the liver cell plates. Their observations may indicate that AASP induces a series of hepatocellular changes culminating in tumor formation. Anthony[63] has reported that liver cell dysplasia is a cytologic representation of a premalignant state. Indeed, sequential changes such as these have been observed in a variety of experimental hepatic tumors.[64]

It has been known for some time that 17-alkylated androgen-anabolic steroid preparations are hepatotoxic.[65,66] The toxicity is usually slight and is detected by abnormalities noted on routine periodic blood test. Uncommonly, jaundice or other clinical signs of hepatic damage appear.

A detailed prospective analysis of liver damage due to methyltestosterone has recently appeared.[59] Of 60 patients taking 150 mg/day of this agent, 19 had at least one abnormality of serum chemistries reflecting liver injury. Of 52 liver scans done, 33 were abnormal with either enlargement of the liver, striking irregularity of the colloid uptake, or both abnormalities. In 11 liver biopsies performed, all demonstrated periportal liver cell thickening. Sinusoidal dilatation, microcyst formation, cholestasis, and migration of hepatocytes into vascular walls were noted in some of the cases. A single large liver adenoma was found in this series.

Peliosis hepatis, a benign proliferation of intrahepatic vascular channels, has been reported in patients taking AASP.[67] Intra-abdominal hemorrhage due to rupture of the cyst can be rapidly fatal.

In summary, idiopathic hepatocellular carcinomas in North America occur more often in males, with a male to female ratio of 1.9 for Caucasian and 2.7 for black patients.[68] Of the 17 reported cases of HCC associated with ingestion of androgen-anabolic steroid preparations reviewed by the authors, 7 had Fanconi's anemia, an extremely rare constitutional disorder characterized by an increased incidence of cancer. Hepatocarcinogenesis is favored by an androgenic environment, both in man and experimental animals (Sections III.B and III.C). Androgen-anabolic steroid preparations commonly cause biochemical, histologic, and clinical evidence of hepatic damage. Consequently, great caution should be exercised in the follow-up care and management of patients receiving these drugs, and they should not be prescribed for trivial reasons to healthy individuals who desire them for their protein-anabolic effect.[69]

Since 1973, close to 100 cases of benign hepatic tumors in young women using oral contraceptives have been reported.[60,69] It is not evident whether residual androgenic activity of progestational compounds could be implicated in the genesis of these tumors. Relationships between hepatic tumors and oral contraceptives are reviewed in Volume I, Chapter 6, by Drill.

2. Incidence of Cancer and Genetic Sex

The effect of genetic sex on cancer incidence can be analyzed at several levels. Differences in rates of organ-specific cancer in males and females are striking, but the immediate biological mechanisms by which genetic sex and its attendant hormonal differences might contribute to them are not established (Table 3).[70]

At the most basic level, differences in sex-organ cancers depend upon events occurring during embryogenesis (Mechanism 6 in Table 1). Phenotypic differentiation as a male following secretion of testosterone by the fetal testes is a necessary but insufficient precondition for subsequent development of cancer in sex-hormone-dependent target organs.[71] Development of cancer at these sites is thought to require continued stimulation of hormone-dependent cells over a prolonged period of time, possibly by a trophic steroid or pituitary hormone (Categories 2, 3, 4, and 5, in Table 1). Reduced synthesis of androgens with increased pituitary secretion of hormones (Category 4, in Table 1) trophic for primary or accessory sex organs occurring over many years may be important for the genesis of some of these cancers but the details are unknown. While there are experimental models available for induction of cancer by thyroid hormones and estrogens, results of attempts to produce cancers with androgens are more ambiguous (Section III.B).

When cancers of the nonsexual organs are considered, any relationship with androgens is even more obscure. Comparison of cancer incidence in children before the onset