Histogenesis and Growth Pattern of 1,2-Dimethylhydrazine-
induced Rat Colon Adenocarcinoma

Alain P. Maskens

Service d’Anatomie Pathologique, Cliniques Universitaires Saint Pierre, 3000 Louvain, Belgium

SUMMARY

The histogenesis and growth pattern of colon adenocarcinoma have been studied using 74 BD IX rats given 20 mg 1,2-dimethylhydrazine hydrochloride per kg, s.c., weekly from Day 11 to their 24th week and serially sacrificed with controls. Modifications in DNA synthesis activity and early tumor changes were sought on histological and radioautographic preparations of normal-appearing colon mucosa. All visible colorectal tumors were analyzed for size, site, and pathology.

Chronic dimethylhydrazine treatments resulted in a simultaneous increase in the number of both total and tritiated thymidine-labeled cells in the glands of Lieberkühn. In addition, microscopic carcinomatous foci were observed after the 15th week, and the first macroscopic adenocarcinomas appeared in 24-week-old animals. Their number thereafter exponentially increased with time. A total of 252 macroscopic tumors were obtained, of which 14 were classified as signet ring cell carcinomas and 238 as adenocarcinomas. Among the latter, local invasion could be documented in 230, including the smallest. No benign polyp-cancer sequence could be demonstrated in this material.

The average growth pattern of those adenocarcinomas could be adequately described by a Gompertz curve, with a short initial doubling time (e.g., 7.5 days in 1.0-cu mm tumors) that progressively increases with time (e.g., 59.6 days in 5000-cu mm tumors).

INTRODUCTION

In recent years, progress in cancer chemotherapy has resulted from a better knowledge of the proliferation kinetics of tumors. In the particular field of solid tumors, important concepts such as growth fraction (25) and cell loss (34) have contributed to a better understanding of their clinical behavior and therapeutic response or lack of response. This stresses the need for extensive kinetic studies in solid tumors of high human incidence.

Stemming from work by Druckrey et al. (14), observations on DMH have recently accumulated indicating that this carcinogen might provide an adequate model for kinetic and therapeutic studies of the colorectal adenocarcinoma, a tumor of increasing frequency in human beings (1). Under certain experimental conditions, DMH induces colon carcinomas in rats and mice with great reproducibility and marked organ specificity (3, 11, 14, 19, 26, 29, 36, 41).

As a first step in the elucidation of the proliferation kinetics of this model, the present study describes the early tumor changes, histology, and growth pattern of the DMH-induced rat colon adenocarcinoma.

MATERIALS AND METHODS

Animals and Treatments

Inbred male BD IX rats (12), graciously provided by Professor H. Druckrey (Freiburg, West Germany) and main tamed on a standard diet and water ad libitum, were used throughout the experiment. Seventy-four animals were given weekly s.c. injections of 20 mg DMH-HCl (Schuchard; Munich, West Germany) per kg; the treatment was initiated between Days 11 and 15 and continued to the 24th week. The DMH-HCl was dissolved in 0.001 M EDTA and brought to pH 6.5 with sodium hydroxide. Twenty-six untreated animals formed the control group. All animals were sacrificed by heart puncture under chloroform anesthesia. There were 3 main experimental groups. In Group A, 2 treated and 2 control animals were sacrificed at 3-week intervals from the 3rd to the 40th week (26 control and 23 treated rats). Forty-five mm prior to sacrifice, they received an i.p. injection of [3H]TdR (Radiochemical Centre, Amensham, England; specific activity, 2 Ci/mmole), dissolved in 0.9% NaCI solution to a final concentration of 100 μCi/ml, at a dose of 0.5 μCi/g of body weight. They were analyzed for changes in DNA synthesis activity in normal-looking mucosa, as well as tumor histology and volume. Group B consisted of 21 treated animals 33 to 40 weeks old serially sacrificed after injection of [3H]TdR with the principal aim of constructing a labeled mitosis curve (which will be reported separately). This group provided additional histological and volume measurement data. In Group C, 10 treated rats were sacrificed at 3-week intervals from the 12th and 21st week; they provided data on early (microscopic) tumor changes. In addition, 3 treated rats were used in testing the tumor volume measurement technique, 6 served for various preliminary experiments, and 11 died spontaneously before the end of the study.
in situ; every tumor or suspicious area was measured for volume and site, resected, and then fixed in 10% formalin. In addition, a specimen of normal-looking mucosa was routinely obtained from the proximal part of the descending colon in all animals of Group A. The remaining abdominal and thoracic viscera were then inspected for macroscopic tumor changes. The tissue samples were embedded in paraffin, and 5-μm sections were prepared. Slides were stained with hematoxylin and eosin, periodic acid-Schiff reagent, and reticulin stain. In the case of tumors, serial sections were obtained whenever necessary to provide adequate observation of the center of the lesions.

**Group C.** Here, the colon was left unopened; approximately 3 cm located at the junction of ascending and descending colon were resected, fixed in 10% formalin, and embedded in paraffin. Step sections 5 μm thick were obtained and each 10th section was analyzed for early tumor changes.

**Volume Measurements**

The 3 main axes of each macroscopic tumor from rats in Groups A and B were measured with a vernier caliper with 0.1-mm graduations. The accuracy of these measurements and their relationship to actual tumor volume were tested in 3 additional rats treated in the same way as the main experimental groups and sacrificed at Weeks 36 (2 animals) and 38 (1 animal), respectively. Each of the 21 tumors present was measured 3 times and then was carefully dissected free of normal surrounding tissue and weighed to the nearest 0.1 mg. These tumors are included in the pathology and growth rate data.

For each Group C animal (early tumor stages), the 2 main diameters of lesions found on serial sections were measured with a Leitz ocular micrometer, the 3rd diameter being estimated from the number of consecutive sections harboring the tumor.

**Development of the Best-Fitting Gompertz Curve**

A Gompertz equation was used to describe the decay of growth rate of the tumors during growth observed in this study:

\[
in V(t) = \ln V(0) + \frac{A}{\alpha}(1 - e^{-\alpha t})
\]

where \( V(t) \) is the tumor volume at time \( t \), \( V(0) \) the initial tumor volume, and \( A \) and \( \alpha \) are adjustable parameters. The Gompertz curve that best fitted the observed data was generated by a method similar to that developed by Simpson-Herren and Lloyd (30). The initial \( \alpha \) value was based on previously reported preliminary data (23).

**Radioautographic Studies**

The specimens of macroscopically normal mucosa of the injection-treated animals of Group A, as well as mucosa from the same site in the controls, were processed for radioautography using the “dipping method” with NTB2 emulsion (Eastman Kodak Co., Rochester, N.Y.). The LI\(^2\) or ratio of labeled to total cells \( \times 100 \), and the labeling pattern were obtained for each specimen by scoring the number and positions of the labeled cells in an average of 20 to 25 histologically normal colonic crypts adequately sectioned from top to bottom. According to the method of Lipkin and Quastler (18), the deepest cell was taken as Position 1, the next as Position 2, and so forth. The labeling pattern was illustrated by plotting the labeled cells per total labeled cells, \( \times 100 \), at the various cell positions in the crypts.

**RESULTS**

**Pathological Findings.** The study yielded a total of 252 macroscopic colon tumors; 238 exhibited a glandular histological pattern. They were constantly observed in each of the 35 rats sacrificed at and following the 24th week. Most (50.2%) were found in the mid-portion of the colon, between the ascending and descending segments (Chart 1), while only 7.2 and 5.5% were in the cecum and distal colon, respectively. Histologically, they were characterized by atypical epithelial cells showing irregular glandular configurations (Fig. 1f). Accessory features such as villi, cysts, inflammatory infiltrate, and fibrosis were present in variable amount. The fibrotic content in some instances accounted for most of the tumor volume. However, there was no good correlation between stroma reaction and tumor size. Using invasion through the muscularis mucosae as a definite criterion for malignancy, 230 cases (96.6%), including the smallest, were determined to be adenocarcinomas. Eight cases were of dubious interpretation, since the histological appearance and cytological changes evoked a carcinomatous rather than adenomatous lesion despite the absence of demonstrable invasiveness. For purposes of simplification, these 8 tumors will be considered, together with the adenocarcinoma group, in subsequent sections of this study.

Fourteen tumors were signet ring cell-infiltrating carcinomas. One of these was present as early as the 18th week. Their average volume was larger than that of adenocarcinomas (805 versus 179 cu mm, respectively). They predominated in the cecum and proximal ascending colon (10 of 14

---

**Chart 1. Distribution of DMH-induced colon adenocarcinomas in BD IX rats.**
cases). While local invasiveness to the mesenteric tissues was regularly demonstrated in large adenocarcinomas, distant metastases were rare and restricted in this experiment to the signet ring cell carcinomas.

In addition to the colon findings, 2 carcinomas were present in the distal ileum, as well as 1 hemangiosarcoma in the liver. No tumors were found in the control animals.

When evidence accumulated that most tumors were adenocarcinomas, that they were first observed in 24-week-old animals, and that they predominated in the midportion of the colon, an attempt was made to trace the early microscopic lesions by analyzing serial sections of that part of the bowel in 10 DMH-treated rats sacrificed between the 12th and the 21st week (Group C). Several abnormal areas were observed as early as the 12th week. These were characterized by the accumulation of undifferentiated cells with pleomorphic nuclei and conspicuous nucleoli in a small cluster of neighboring crypts ("atypias"). In the 8 animals sacrificed between the 15th and the 21st week, more specific changes could be observed. Sixteen lesions exhibiting cytological changes as seen in atypias as well as severe distortion of the glandular shape were highly suggestive of in situ carcinoma (Fig. 1c). Their sizes were less than 0.1 cu mm. Four additional lesions, larger in size (0.2 to 1.3 cu mm), further demonstrated early invasion through the muscularis mucosae (Fig. 1d and e). The frequency of both types of microscopic carcinomas was age related. Similar microscopic changes were also occasionally observed in samples of macroscopically normal mucosa from older animals of Group A, with increasing frequency in later sacrificed rats.

Volume Measurements. In a control group of 21 macroscopic tumors, a linear correlation was calculated between the products of the 3 main axes (cu mm) and the actual volumes as determined by the weight (mg) (assuming density = 1). A correlation coefficient of 0.69 was found. It is intermediate between the coefficient for cylinders (0.79) and for ellipsoids (0.52). In the same group of tumors, the accuracy of the caliper measurements was evaluated by comparing the products of 3 different measures of the axes of the same tumor with their respective mean. The median error was 5.75%. The median error between the actual weights and the volumes calculated using the above coefficient was 13.75%. This coefficient was subsequently used in calculating the volumes of all macroscopic tumors in this study.

In the case of microscopic carcinomas, however (Group C), the axes product as such was taken as an estimate of the actual volume, since they were all ellipsoid in shape, and in order to compensate for the average 20% linear retraction that occurs in those tissues during histological procedures.¹

Growth Rate Studies. As opposed to s.c. transplanted tumors or tumors of superficial organs (skin, breast), individual tumors of the colon cannot be serially measured without considerable risk of disturbing their natural environment and hence growth characteristics. Based on the observation of the macroscopic tumor sizes and number at the various times of sacrifice, several deductions could however be made, leading to an approximation of the average growth rate of these tumors. Only adenocarcinomas are taken into account. First, it is obvious that the number of tumors per animal increases with time (Chart 2). This relationship is nonlinear, and can be approximated by logarithmic regression analysis:

\[ \ln N(t) = -2.419 + 0.0178 t \]

where \( N = \) number of tumors, \( t = \) time in days from birth of the animal, and \( r = 0.6677 \). Second, tumor sizes also increase with time, as illustrated when the volume of the largest tumor present in each animal is plotted against time of sacrifice (Chart 3). It evokes an exponential-type growth, the rate of which can be obtained by regression analysis:

\[ \ln V(t) = -1.481 + 0.032 t \]

where \( V = \) tumor volume in cu mm, \( t = \) time in days from birth of the animal, and \( r = 0.6051 \). The corresponding doubling time is 22.0 days. Third, when several carcinomas are present in 1 colon, their sizes are not uniform but, rather, are graded. Since tumor number and volume are both positively correlated with time, one can postulate that, in the same animal, the largest tumor arose first, followed by the 2nd largest tumor, etc. Accordingly, the exponential growth rates were computed for each set of homologous tumors (i.e., plotting the log volume of the largest tumor of each animal versus the time of sacrifice, then the same for the 2nd largest tumor, etc). As a matter of fact, these rates are remarkably comparable from one tumor group to the other (Chart 4). This indicates that, notwithstanding variations between animals, different tumors in the same animal have quite similar growth behaviors, with however a somewhat faster growth rate in small tumors.

The possibility that smaller tumors grew more rapidly led us to speculate that those DMH-induced rat colon adenocarcinomas could be characterized by a Gompertz-type growth pattern (23). Although this can hardly be demonstrated over the observation range of the macroscopic tu-

---

¹ Indeed, if a, b, and c, are the actual axial measures, those obtained on histological sections will be approximately 0.8a, 0.8b, 0.8c, and (0.8a) × (0.8b) × (0.8c) ~ 0.52 × (a×b×c).
A. P. Maskens

Chart 3. Linear regression of the volume of the largest adenocarcinoma (logarithmic scale) present in each DMH-treated rat colon (Group A and B animals) versus time of sacrifice (days from birth). Point with vertical bars, mean value ± S.E. for 15 animals from Group B, all sacrificed the same day; other points, 1 animal each.

Chart 4. Linear regressions obtained for the successive sets of homologous tumors (Group A and B animals). 1, regression of the volume of the largest adenocarcinoma (logarithmic scale) per animal versus time of sacrifice, as shown in Chart 3. 2 to 9, regression of the 2nd to 9th largest tumor per animal.

Chart 5. Volume of the largest adenocarcinoma (logarithmic scale) in the colon of DMH-treated rats versus time of sacrifice (days from birth). Microscopic carcinomas observed in younger animals (Group C) are plotted together with the macroscopic measurements obtained in older animals (Groups A and B). The line represents the best-fitting Gompertz curve. Each point, 1 animal.

Chart 6. Total number of cells, number of labeled cells, and percentage of labeled cells per column of crypt cells in histologically normal colon glands from normal and DMH-treated animals sacrificed 45 minutes after i.p. injection of [3H]Tdr. The specimens were all obtained from the proximal descending colon. Each point, mean value from an average 46 crypt cell columns scored per animal. The dashed and solid lines are linear regressions of the control and DMH data, respectively. Covariance analysis indicate that the 2 groups differ significantly in the number of labeled cells (p < 0.01) and total cells (p < 0.01) per crypt column. △, labeled cells, normal; ●, labeled cells, DMH; ○, total cells, normal; □, total cells, DMH; O, Ll, normal; ●, Ll, DMH.

The best-fitting Gompertz curve is given by:

$$\ln V(t) = -4.14 + 0.135(1 - e^{-0.0095t})$$

where \( V = \text{cm}^3 \); \( t = \text{days} \); \( t(0) \) arbitrarily set at 15 weeks after birth, when the earliest microscopic carcinomas can be observed; and \( r = 0.9431 \).

Radioautographic Findings. The mean number of total and labeled cells per crypt cell column and the LI in histologically normal colon glands from normal and treated rats (Group A) are reported for 9 times intervals between the 15th and the 40th week (Chart 6). In normal rats, the depth of the glands as expressed by the total cell number per crypt was found to be quite stable, with a slow but significant increase with time (\( r = 0.5902, p < 0.005 \)). The number of labeled cells varies more from one specimen to the other, with again a slow increase with time (\( r = 0.4215, p < 0.05 \)). Consequently, the LI shows individual variability, but remains stable with time (\( r = 0.2856, p > 0.10 \)). In the group of DMH-treated animals, the total number of cells per crypt similarly exhibits a slow increase with time (\( r = 0.5666, p < 0.005 \)); the correlation between number of labeled cells and time is not significant (\( r = 0.3304, p > 0.10 \)). As a result of DMH, however, the numbers of both total and labeled cells are significantly higher than in the control group (respective means: \( 51.52 \pm 2.35 \) (S.E.) versus \( 37.45 \pm 0.85 \) total cells
MAY 1976 1589

Since these modifications occur in parallel, there is no net change in their relative proportions, and the LI in injection-treated animals was found in the lower two-thirds of the crypts (mean values: normal, 99.2%; injected, 98.4%) (Fig. 1a). However, because of the increased labeled and total crypt cell number in the treated animals, the proliferative compartment occupies a larger number of cell positions in the latter than in controls (Chart 7). The mean position of the uppermost labeled cell per crypt column in each group is, respectively, 23.01 ± 1.36 (S. E.) and 15.76 ± 0.71 (p < 0.01). Labeled cells were never found at the luminal surface of histologically normal mucosa.

The labeling pattern in histologically normal glands was also found comparable in control and treated animals. In both, nearly all the nuclei engaged in active DNA synthesis were found in the lower two-thirds of the crypts (mean values: normal, 99.2%; injected, 98.4%) (Fig. 1a). However, because of the increased labeled and total crypt cell number in the treated animals, the proliferative compartment occupies a larger number of cell positions in the latter than in controls (Chart 7). The mean position of the uppermost labeled cell per crypt column in each group is, respectively, 23.01 ± 1.36 (S. E.) and 15.76 ± 0.71 (p < 0.01). Labeled cells were never found at the luminal surface of histologically normal mucosa.

The above data refer only to chronic changes induced by DMH, since those animals were sacrificed more than 4 days after treatment. However, at the 3rd, 7th, 13th, and 24th week, the animals were sacrificed from 4 to 6 hr after treatment with DMH. Acute toxicity was evidenced by the presence of numerous karyorrhectic figures, and a decrease in DNA synthesis activity (mean LI, 7.29%). These results therefore were excluded from the main labeling data.

As noted earlier, several microscopic lesions were occasionally found in these [3H]Tdr-labeled specimens of macroscopically normal mucosa. In atypias, the epithelial cells constantly exhibited a high thymidine uptake which was more pronounced in the deeper portion of the glands than in the vicinity of the surface epithelium (Fig. 1b). In microscopic carcinomas, labeled cells were present throughout the lesion.

**DISCUSSION**

Two major classes of chemical carcinogens with marked organotropism for the lower gut are currently under investigation (38), namely, the aminobiphenyl derivatives introduced in 1952 by Walpole et al. (37) and the dialkylhydrazines and azoxyalkanes introduced by Druckrey et al. (14) in 1967. The latter are related to the aglycone of cycasin, which Laqueur (17) in 1965 described as causing intestinal tumors in rats. With accumulating evidence that the 2nd group, and particularly azoxymethane and DMH, constantly exhibits a high and specific colon tumor yield, these compounds are of promising value for developing colon cancer models for kinetic and therapeutic studies. The latter was chosen for its apparently shorter induction time as compared to azoxymethane at nontoxic doses (11).

Among the various research groups who published on DMH and despite differences in doses, schedules, and animal strains, several consistent findings emerge (11, 14, 19, 36, 40, 41). When DMH is given on a weekly basis and the induction time is sufficient (16 to 24 weeks), 100% of the animals present with tumors. These occur predominantly in the large bowel. In rats, they appear as discrete tumors distributed in the ascending and descending colon while, in mice, there is diffuse involvement of the distal colon and rectum. The most commonly found neoplasm is an adenocarcinoma. Variation can occur in the induction time, the extent of the extra-colonic lesions, and the presence of benign polyps. Several factors capable of inducing these variations have been identified. While a single dose of azoxymethane or DMH produces tumors in some of the treated animals, the yield on a weekly schedule is constant (13, 19, 21). With increasing doses of DMH, the latency period is shortened (11), and the yield in small bowel tumors is possibly enhanced (11, 40). Genetic susceptibility is suggested by a lower tumor production in BD II rats as compared to BD IX (3). Age also plays a role, since differences in organotropism and tumor yield were demonstrated after a single dose of azoxymethane or DMH was given at various intervals after birth (21). Finally, the bacterial content of the gut as well as the dietary fat level were recently shown to influence tumor production in DMH-treated rats (27, 28). Therefore, in order to minimize individual variability, the present model has been developed using male rats of the inbred BD IX strain, fed a standard diet, and given a standard and prolonged DMH treatment.

Under these experimental conditions, the DMH-BD IX model appeared to be highly reproducible. Indeed, after a 24-week induction period, macroscopic tumors were present in 100% of the treated animals. Of these tumors, 91% were glandular and locally invasive, thus constituting a uniform group on a pathological basis. They constantly predominated in the mid-portion of the colon. In spite of individual variations, clear correlations were observed between tumor volume or number, and time. These properties allowed the early tumor stages to be traced and the average growth pattern of this colon adenocarcinoma to be defined.

The first recognizable significant lesions were small clusters of irregularly shaped glands consisting of poorly differentiated epithelial cells with nuclear atypias. They were seen as early as the 15th week. Several such microscopic carcinomas clearly demonstrated invasiveness through the muscularis mucosae, as did 97% of the macroscopic lesions observed after the 24th week. These findings seem to indicate that, in this particular experimental system, most le-
sions are carcinomatous from their beginning, with no prior benign polyp stage. Some authors reported that both amniobiphenyl and DMH derivatives can give rise to benign polyps as well as carcinomas (26, 32, 36, 40). Our data however agree with those of Wiebecke et al. (40) who claimed that most of the tumors induced by DMH in rats and mice colon were malignant, and described frequent "microcarcinomas" with early infiltration. Likewise, Thurnher et al. (36) and Deschner (5) described in situ carcinomas in mice given weekly DMH. These observations represent strong evidence that adenocarcinomas can arise de novo in the colon mucosa. It is stressed however that this conclusion is relevant only to carcinogen-induced tumors in rodents, and can document at most the theoretical possibility of such mechanisms in humans.

In a preliminary attempt to illustrate changes induced by DMH prior to tumor formation, [3H]TdR incorporation in histologically normal colon mucosa of treated rats has been studied. Chronic treatment produced an enlargement of the proliferative pool in the colonic crypts, in accordance with other such radioautographs in rodents (19, 36, 40). In contradiction to those studies however, no modifications in the relative distribution of labeled nuclei in the crypts were observed. An elongation of the normal crypts concomitantly occurred, which finding was also reported by Springer et al. (33). The exact relationship between the increase of the proliferative pool, a diffuse phenomenon, and the focal occurrence of carcinomas probably bears crucial significance in the understanding of colon carcinogenesis. It is hoped that further studies using the DMH model will contribute some progress in this matter. Of related interest is the possible analogy between the present observation and the extension of the proliferative pool reported in human lesions susceptible to malignant change, such as chronic ulcerative colitis (2), adenomatous polyps and villous adenomas (7, 8, 22), and familial polyposis (4, 6).

After the tumors have been induced, their average behavior can be accurately described by 2 major properties: the tumor increment with time is exponential, and the growth pattern is of the Gompertz type. Data by Deschner (5), who counted the number of focal atypias present in 0.5 mm of mice distal colon mucosa at different DMH treatment periods, similarly demonstrated a nonlinear increase with time. This phenomenon possibly bears a relationship to the additive nature of the DMH treatments. After Laird (16) used the Gompertz equation to express the decaying growth rate of tumors and normal organisms, several human and experimental tumors could be fitted into this particular growth pattern (15, 24, 30, 31, 35). In the present model, if one considers that the curve had to be generated from measurements on different tumors instead of serial measurements of the same tumor, the fit of the curve to the data is satisfactory, thus allowing the estimation of the age and doubling time of a tumor of given volume. This was a mandatory prerequisite for further kinetic studies in such a model where direct measurements of tumor growth cannot be obtained.

The possibility has to be raised that the faster growth rate observed in small size carcinomas as illustrated on Chart 5 is artifactual, since tumors measured up to the 24th week could have been influenced by the weekly DMH treatments.

In addition, data obtained using 2 different measurement methods (microscopic and macroscopic) are grouped together. However, small macroscopic carcinomas observed in older animals, after the treatments have been interrupted, do exhibit a similarly faster growth rate as well (cf. Chart 4).

The implications of the computed Gompertz function are manifold. The first carcinomas can be recognized in rats 15 weeks old, with a theoretical initial volume of 0.016 cu mm, equivalent to a sphere 313 µm in diameter, or a small cluster of transformed crypts. If those tumors evolve from a single transformed cell, the average period at which the first such transformation occurs can be predicted to be about 50 days after birth by extrapolating the curve to the 1 cell volume. The theoretical maximum volume is 24,861 cu mm, not far from the largest tumor volume (35,000 cu mm) actually observed in an ongoing study on long-term survivors (unpublished data). It should be stressed, however, that extrapolating extreme values from a Gompertz function is hazardous (10), much more so in this study, where the curve merely represents an average estimate. Finally, the tumor-doubling time, which is low in small tumors (e.g., 7.5 days in 1.0-cu mm tumors), rises with size (e.g., 25.6 days in 1000-cu mm tumors) and eventually reaches values that approach human data more closely than other experimental solid tumor systems (30), emphasizing the appropriateness of this model for further kinetic and, possibly, therapeutic studies.

From serial radiographic observations, We!in et al. (39) showed that human colorectal cancers usually demonstrate a slow exponential volume increase. In the present model, also, large tumors have a comparatively slow growth rate which varies little with time, thus mimicking an exponential curve. This however cannot be extrapolated to small tumors, where the volume increase is rapid and the growth rate much more variable with tumor age or size. Thus the possibility exists that human colon carcinomas might also be characterized by a Gompertzian growth, with short-lived precocious stages and persistent, more slowly evolving large lesions. If such a growth pattern could be verified in human pathology, it would perhaps explain why very small, or de novo human colon carcinomas are rarely described in the literature. It would also imply that patients with high risk of colorectal cancer be submitted to medical followup at frequent intervals, if early lesions are to be detected. Emphasis should be put on the development of new methods of early colon cancer detection, such as exfoliative cytology and studies of [3H]TdR incorporation in colon washings (9, 20).

ACKNOWLEDGMENTS

The author wishes to thank Professor Meersseman, Dr. Haot, and Dr. Rahier for continued interest and discussions; Dr. M. Lipkin and Dr. E. E. Deschner for reviewing the manuscript; R-M. Loits, B. De Neuter-Maskens, and H. Withofs for skilled assistance; and F. Gennart for helpful secretarial assistance.

REFERENCES

2. Bleiberg, H., Mainguet, P., Galand, P., Chretien, J., and Dupont-Mairesse,

1590

CANCER RESEARCH VOL. 36


Histogenesis and Growth Pattern of 1,2-Dimethylhydrazine-induced Rat Colon Adenocarcinoma

Alain P. Maskens


**Updated version**
Access the most recent version of this article at:
[http://cancerres.aacrjournals.org/content/36/5/1585](http://cancerres.aacrjournals.org/content/36/5/1585)

**E-mail alerts**
Sign up to receive free email-alerts related to this article or journal.

**Reprints and Subscriptions**
To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.

**Permissions**
To request permission to re-use all or part of this article, contact the AACR Publications Department at permissions@aacr.org.