

Statement by Sidney M. Wolfe MD  
Public Citizen's Health Research Group\*

Biomarkers for Screening, Diagnosis and  
Treatment of Cancer:  
Why Not for Harm Prevention as Well?  
A Case Study Involving ACF/orlistat  
Institute of Medicine

Committee on Developing Cancer Biomarkers  
June 15, 2006

Prepared with input from Elizabeth Barbehenn, PhD\*,  
Theresa Pretlow, PhD, and Thomas Pretlow, MD

The title of the March IOM workshop which gave rise to this committee was “Developing Biomarker-based Tools for Cancer Screening, Diagnosis, & Therapy”, implicitly ignoring those biomarkers related to externally caused harm.

However, the Biomarkers Definitions Working Group recently “Proposed a general definition of a surrogate end-point as a biomarker that is intended to substitute for a clinical end-point and is expected to predict clinical benefit (**or harm** or lack of benefit) based on epidemiological, therapeutic, patho-physiological, or other scientific evidence.”

**Biomarkers Definitions Working Group. Biomarkers and surrogate endpoints: preferred definitions and conceptual framework. Br. J Clin Pharmacol Ther 2001, 69, 89–95.**

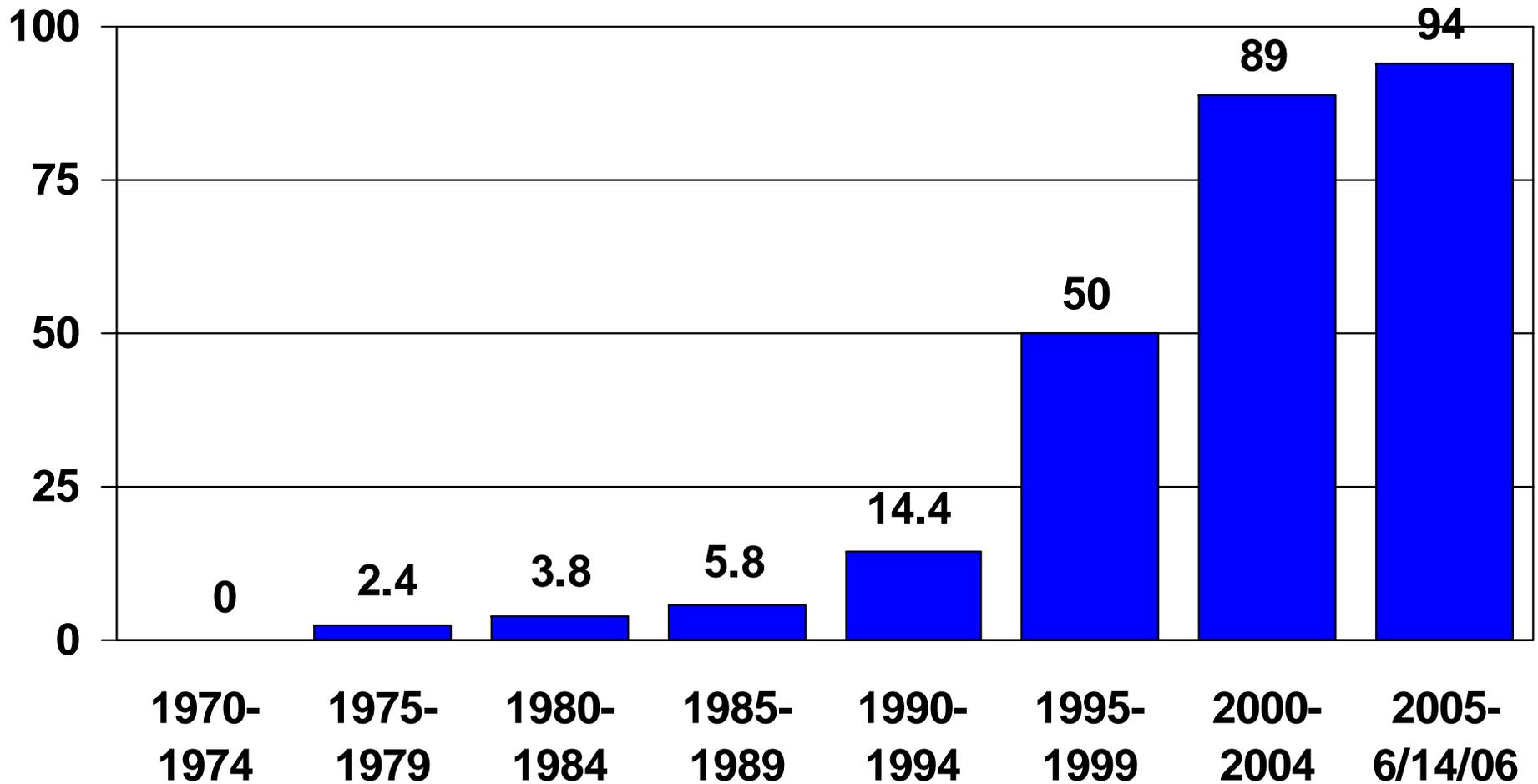
# Evidence of a Double Standard for Biomarkers

- Finding markers for predicting clinical benefit (screening/treatment) seems to have trumped the search for markers that predict clinical harm.
- Even when a biomarker is valid enough to be used, as in ACF, for finding chemoprevention agents for colon cancer it is not yet actively used to predict harm.
- We hope your committee seriously considers the importance of this other aspect of biomarkers—those that can be used to predict harm---as stated by the Biomarkers Definitions Working Group.

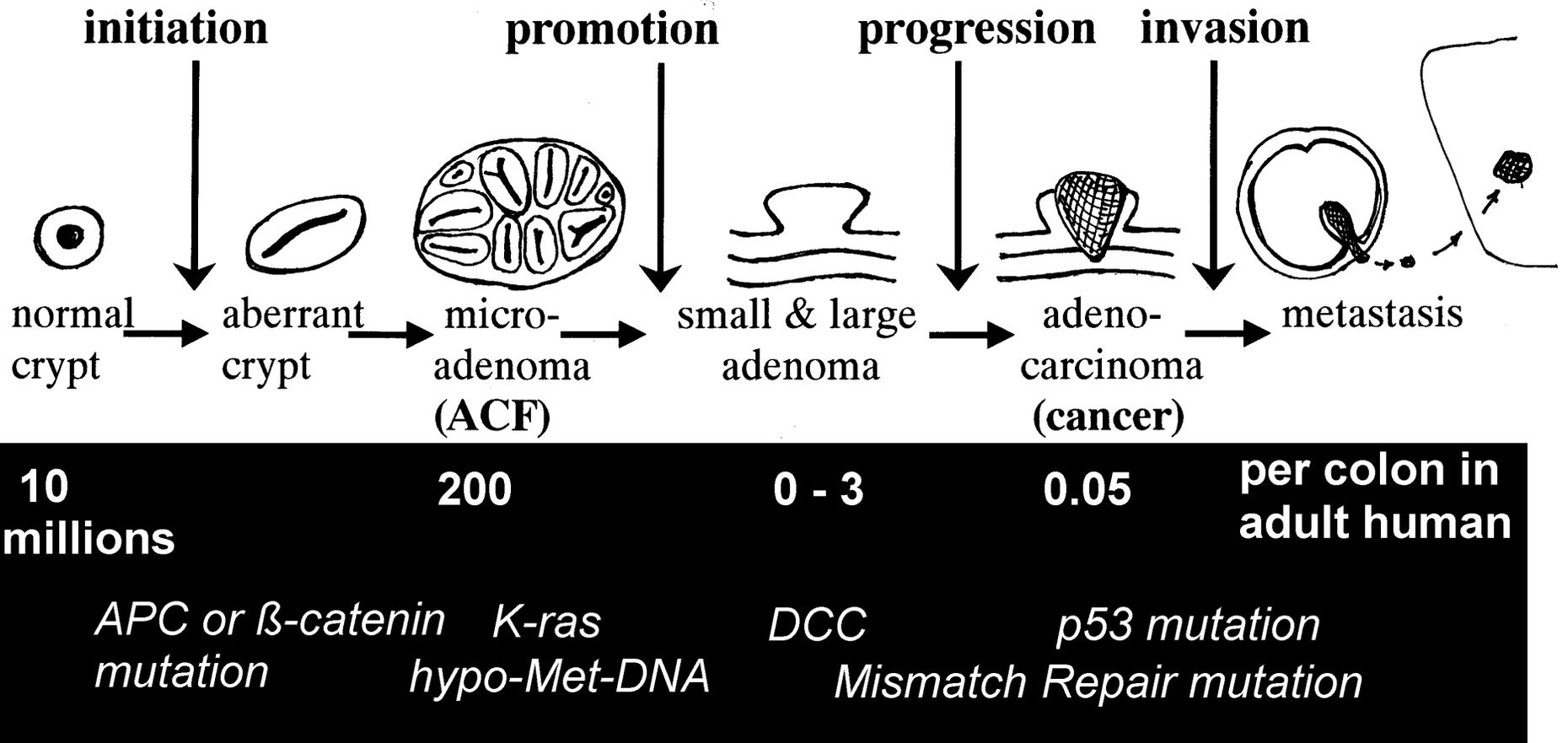
# Topics to be covered today

- Review of ACF: evidence for this neoplasm as a precursor of colon cancer
- Just-published clinical study linking ACF to colonic advanced neoplasms
- Two animal studies showing orlistat increases ACF but inadequate 2-year carcinogenicity studies
- FDA guidelines that would include ACF but which have not been implemented for orlistat
- Summary of the double-edged sword/double standard for biomarkers

# Publications Per Year\* Concerning Aberrant Crypt Foci (ACF)



\* Source: Medline



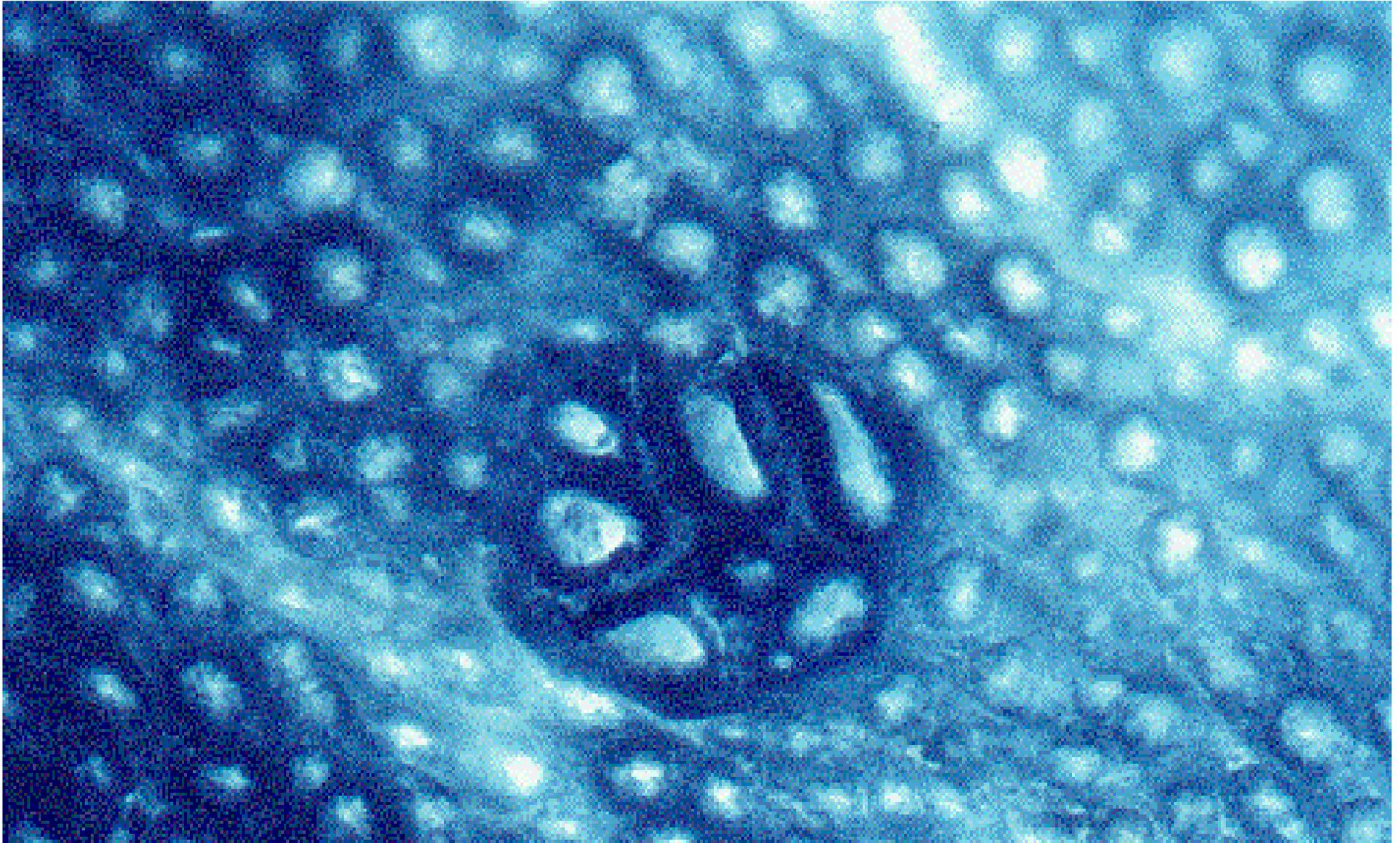
<http://www.inra.fr/reseau-nacre/sci-memb/corpet/acfprogd.gif>

# Characteristics of ACF

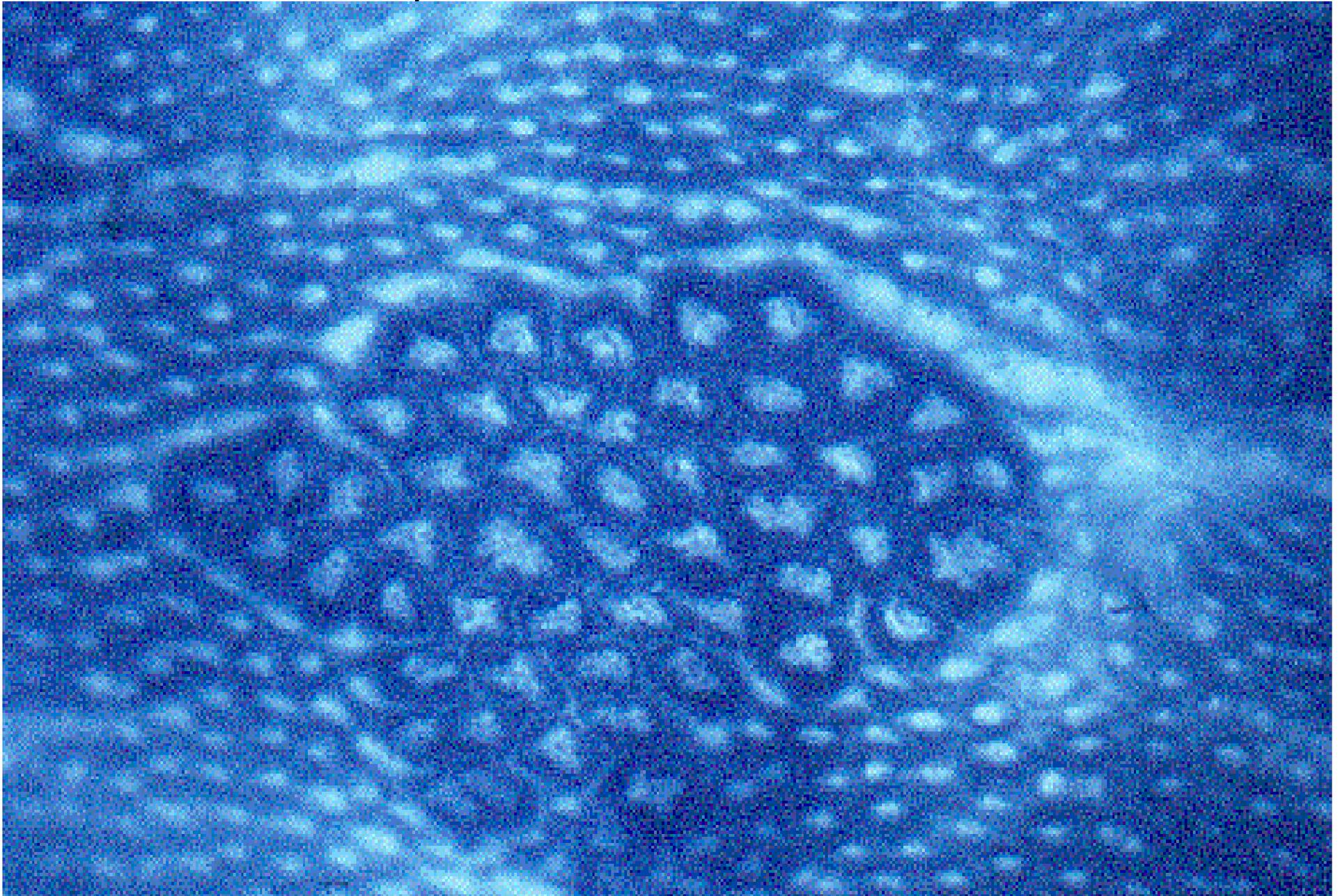
Crypts in ACF:

- are two to three times larger than normal crypts,
- are microscopically elevated,
- have a slit-like opening,
- have a thick epithelial lining that stains darker than normal crypts, with a large pericryptal zone.

The normal crypts appear as circular structures each with a small luminal opening. In this field we see a focus of aberrant crypts [6 large ones, 1 small] that appear to be forming a single (ACF) unit.



This is a large human ACF. Note the luminal openings are often more varied in shape than those seen in rodents.



# Further characteristics of ACF

- Induced by colon-specific carcinogens in a dose dependent manner
- Each evolves from one altered cell
- Are neoplastic, sharing characteristics in common with colon cancers (mutations of specific genes, dysplasia, and abnormal proliferation)
- Size and number of crypts per focus increase with time
- Features predict tumor outcome and risk
- More likely to be present in individuals at high risk for colon cancer

The connection of ACF with carcinogenesis is so well recognized that the appearance of ACF in rats is used by many groups to test the potential carcinogenicity of chemicals. For example, the Environmental Protection Agency (EPA) uses an ACF assay in its tests of possible carcinogens. The ACF assay is also routinely used to examine compounds that may prevent cancer, i.e., prevent ACF formation.

# Further Evidence of the Clinical Significance of ACF Formation

- In a paper entitled the “Role of aberrant crypt foci detected using high-magnification chromoscopic colonoscopy in human colorectal carcinogenesis”, Hurlstone concluded that:
- “From a practical perspective, although only a small number of ACF will ultimately progress to CRC, larger ACF with altered morphology, dysplastic histology and associated gene mutations remain high-risk candidates for adenoma and CRC formation.”

# Possible Role of ACF in Chemoprevention Research

According to Niitsu, et al, “ACF should be appropriate chemopreventive targets in colorectal cancer. The advantages of using ACF as targets over using polyps are as follows:

- 1/ short-term treatment for evaluation
- 2/ fewer complications caused by drugs
- 3/ good compliance”

“we have previously reported that the number of ACF is markedly reduced after treatment with sulindac for about 1 year”

## **Patients at different stages of colon cancer and their relative risk of having dysplastic ACF \***

<b>Patients at different stages of cancer</b>	<b>Relative risk</b>
None (normal)	1.0 (reference)
Adenoma	4.0
Cancer	18.0

**\* Dysplastic ACF with compressed/ indistinct lumen and a much thicker lining**

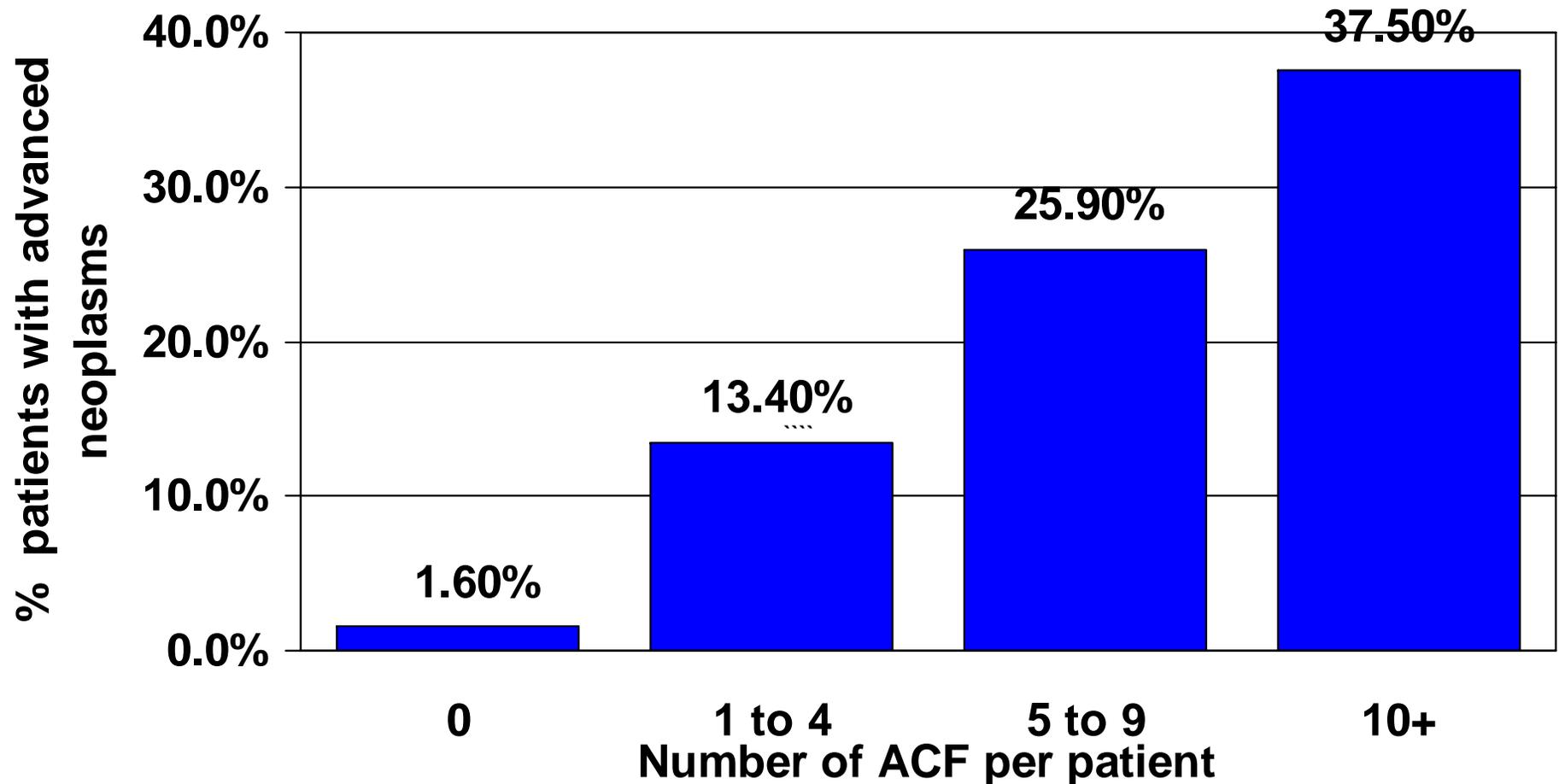
**Takayama T, Katsuki S, Takahashi Y, et al. Aberrant crypt foci of the colon as precursors of adenoma and cancer. *New Engl J Med* 1998;339:1277-1284.**

## Relation of stages leading to human colon cancer and the number of crypts per focus

<b>Stage of cancer</b>	<b>Median number of aberrant crypts per focus</b>
None (normal)	1 (reference)
Adeno ma	9
Cancer	38

[1] Hurlstone DP, Karajeh M, Sanders DS, et al. *Am J Gastroenterol* 2005;100:1283-1289.

# Relationship between the Number of ACF and Advanced Colonic Neoplasms in 386 Patients



Seike, et al. Assessment of Rectal Aberrant Crypt Foci by Standard Chromoscopy and its Predictive Value for Colonic Advanced Neoplasms  
Am J Gastroent June, 2006;101:1362

**Table 5.** Age- and Gender-Adjusted Multivariate Analysis of Independent Factors for Present or Past Rectal Neoplasms

Variable		Prevalence	Adjusted OR (95% CI)
Advanced neoplasm			
grade	0	1/63(1.6%)	1 (reference)
	1	15/119(12.6%)	8.97 (1.15–69.86)
	2	32/116(27.6%)	23.72 (3.13–179.66)
	3	21/88(23.9%)	19.33 (2.47–151.12)
Invasive cancer			
grade	0	1/63(1.6%)	1 (reference)
	1	8/119(6.7%)	5.08 (0.61–42.42)
	2	10/116(8.6%)	6.86 (0.83–56.48)
	3	9/88(10.2%)	8.83 (1.03–76.09)

OR = odds ratio; CI = confidence interval.

# FDA Review of Unpublished Roche Study of Orlistat from 1996

- “There was a treatment-related increase in the number of colonic aberrant crypt foci noted in mid- and high-dose females..” .... This increase in ACF occurred even though the highest doses used in this study were only 40% (males) and 60% (females) of the human exposure.
- as a result, “The reviewing pharmacologist is advised to take such an inadequacy of the design into account in the determination of the carcinogenic potential of this drug,”

**FDA Pharmacology and Statistical reviews  
of orlistat, 1997**

# Additional Concerns about Orlistat Due to its Significant Effect on Vitamin E Depletion

In addition to ACF formation promoted by orlistat, is evidence that because it inhibits the absorption of fat-soluble vitamins such as vitamin E, this may also increase the risk of colon cancer. A September, 1997 paper published in Cancer Causes Control stated that a review of the relationship between colon cancer and vitamin E concluded that 'a randomized clinical trial, a cohort study, and a case-control study have all found inverse associations between colon cancer and vitamin E.'

“The anti-obesity agent Orlistat is associated [with] increase in colonic preneoplastic markers in rats treated with a chemical carcinogen”

- the number of ACF per cm<sup>2</sup> was increased 60% in rats fed orlistat or in rats fed a high fat diet (without orlistat).
- This number was further increased, however, to 2.4-fold in the group receiving both high fat and orlistat (the baseline being rats fed a low fat diet and no orlistat).

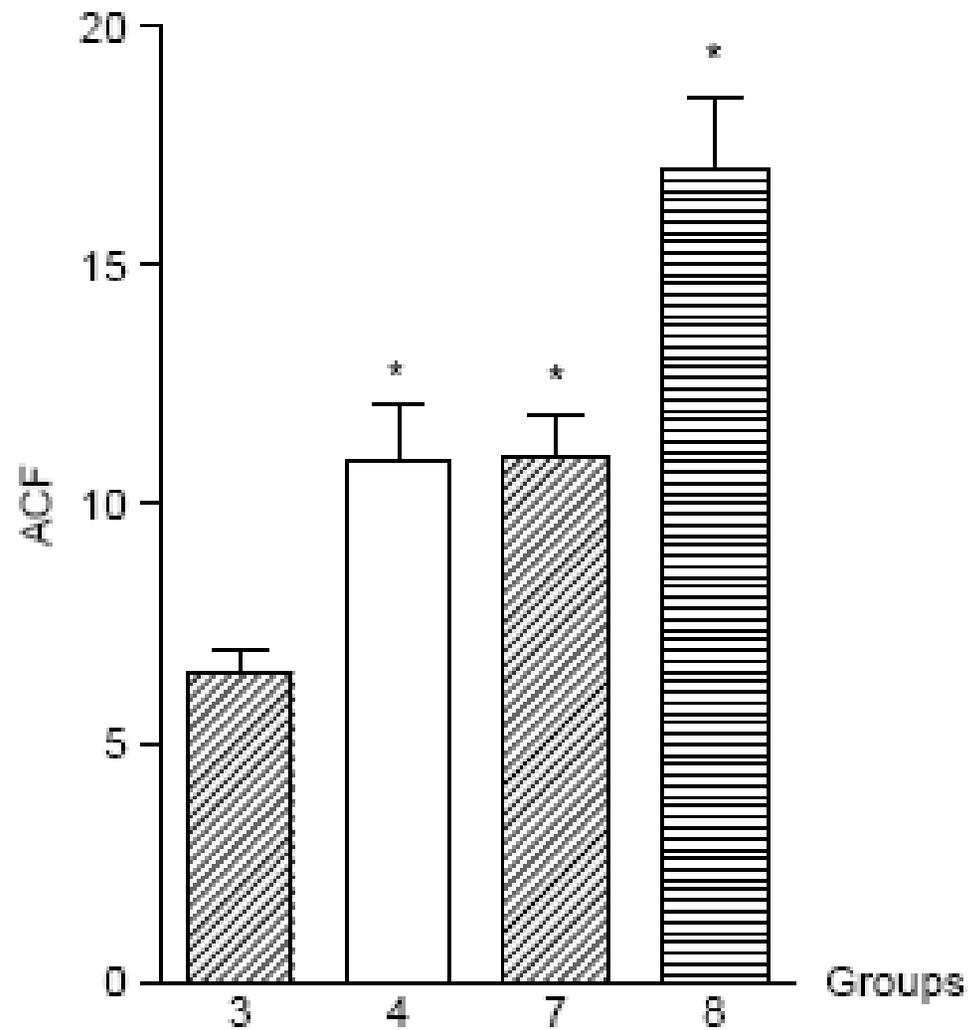


Fig. 1. Number of aberrant crypt foci per cm<sup>2</sup> of rat colon mucosa in animals treated with dimethyl-hydrazine. Group 3 received standard rat food; Group 4 received standard rat food and Orlistat; Group 7 received high fat diet and Group 8 received high fat diet and Orlistat. \*8 > 7 = 4 > 3 ( $P \leq 0.05$ ).

# Current FDA Policies on Carcinogenic Risk Evaluation\*

- Among reasons for conducting a [valid] animal carcinogenicity test is “evidence of preneoplastic lesions in repeated dose-toxicity studies”
- Questions for making approval decisions include
  - a/ are findings relevant to humans?
  - b/ multi-species evidence for carcinogenicity?
  - c/ are alternative drugs not carcinogenic?

**Human Carcinogenic Risk Evaluation, Part III: Assessing Cancer Hazard and Risk in Human Drug Development. *Toxicological Sciences*. 81, 260–262 (2004)**