

A Human Model of Gastric Carcinogenesis¹

Pelayo Correa

Department of Pathology, Louisiana State University Medical Center, New Orleans, Louisiana 70112

Animal models of carcinogenesis have contributed substantially to our understanding of neoplastic and preneoplastic events. Typically, laboratory experiments seek specific information on suspected carcinogenic agents and for that reason usually focus on one agent at a time. To test the suspect agent, an adequate yield of neoplastic lesions is desirable, usually several orders of magnitude greater than the frequency observed in humans; that requires the administration of doses many times greater than those prevailing in most human situations. The high yield also requires that animal strains be selected which have a proven susceptibility to the compound, thus concentrating on genetically homogeneous (often inbred) populations of experimental animals. These experimental requirements contrast with most human situations in which mixed, low-dose, carcinogenic influences act on genetically heterogeneous populations. This high-yield high-dose requirement also restricts the study of the precancerous process since it is purposefully accelerated and, therefore, provides insufficient time and opportunity to observe the precursor stages which may be better expressed in humans. In animal models some of the precancerous changes are observed only when lower doses of weaker carcinogens are used (1).

The study of human models of carcinogenesis has begun in recent years. Of necessity, they are based on epidemiological and laboratory observations under circumstances which cannot match the rigorous specifications of experimental designs. However, recent progress in techniques applicable to the human studies now make it possible to test specific links in the chain of events leading to neoplastic transformation of human tissues. To illustrate these points, a proposed model for gastric carcinogenesis in humans will be presented, based on epidemiological, pathological, and clinical observations.

Etiological Model

Morphological observations on the human stomach have been accumulating in several countries for more than a century. They have, among other things, led to two major conclusions. (a) There are at least two distinct clinicopathological entities covered by the name "gastric carcinoma." One is called "intestinal" or "expansive" type, which predominates in high-risk populations ("epidemic type"), and is preceded by a prolonged precancerous process. The second type, usually called "diffuse," or "infiltrative," is relatively more frequent in low-risk populations and is not preceded by well-defined precancerous lesions (2, 3). (b) The precancerous stages of the intestinal type, which are the subject of this review, represent a very complex process, part of which results in a transformation of the normal mucosa into an intestinal type of mucosa (Fig. 1). Observations in several populations at high gastric cancer risk have documented a series of lesions which are more severe and more extensive in older individuals, leading to the hypothesis that they form a

continuum which reflects increasingly regressive phenotypical changes (4, 5). The morphological changes observed fall into three categories: inflammation, atrophy, and loss of cellular differentiation. The inflammatory changes (chronic gastritis) are more accentuated in younger individuals and become progressively less conspicuous with age, although persisting throughout most of the process. Atrophy, or gland loss, becomes more advanced and conspicuous with age; in extreme situations the gastric mucosa becomes practically devoid of its original glands. The loss of differentiation in reality appears to represent successive mutations (or similar changes in the genetic material of the cells), since the gastric epithelial cells disappear as such and are replaced by cells with intestinal phenotype; the daughters of these "mature" intestinal cells then display apparently progressive phenotypic changes, lose some of their normal cytoplasmic secretions and gain autonomy, which eventually leads to uninhibited replication and invasion of the neighboring tissues. These changes are outlined in the right-hand column of Fig. 1.

Phenotypic Changes

The first steps in the process (inflammation and atrophy) do not change the normal phenotype of the gastric epithelial cells: they involve cell loss and cell regeneration, processes that are normal in the gastrointestinal epithelium and only become exaggerated when the forces responsible for the atrophic gastritis set in. Some of these forces or factors have been identified in epidemiological studies as irritants and as a suboptimal supply of micronutrients (6-8). After the step of atrophy, the forces involved in the process apparently require the presence of genotoxic agents, since at this stage hereditary cellular changes are implied which should represent changes in the structure or function of nuclear DNA. It has been proposed that these mutagenic agents are synthesized *in vivo* in the stomach by the action of nitrite on nitrogen-containing organic compounds (4). Nitrite is abundant in the gastric cavity of subjects with atrophic gastritis, at least partially as a result of bacterial reduction of dietary nitrate. In addition, nitrate and nitrite may be produced by macrophages, which are also present in chronic gastritis (9). The synthesis of nitroso compounds and the cellular damage that they may cause are probably modulated by other compounds present which may act as facilitators of carcinogens (10, 11) or as inhibitors through antioxidant or similar roles (12).

The following paragraphs will examine scientific evidence relevant to the morphological changes proposed and the etiological factors implicated in their appearance.

Chronic Atrophic Gastritis and Intestinal Metaplasia

Loss of gastric glands (chronic atrophic gastritis) and their replacement by intestinal-type epithelium has been recognized in humans for more than a century (13). It has been repeatedly demonstrated that metaplastic glands surround practically all carcinomas of the intestinal type which have been studied for

Received 1/13/88; accepted 3/24/88.

¹Work supported by Program Project P01-CA-28842 from the National Cancer Institute, NIH, Bethesda, MD.

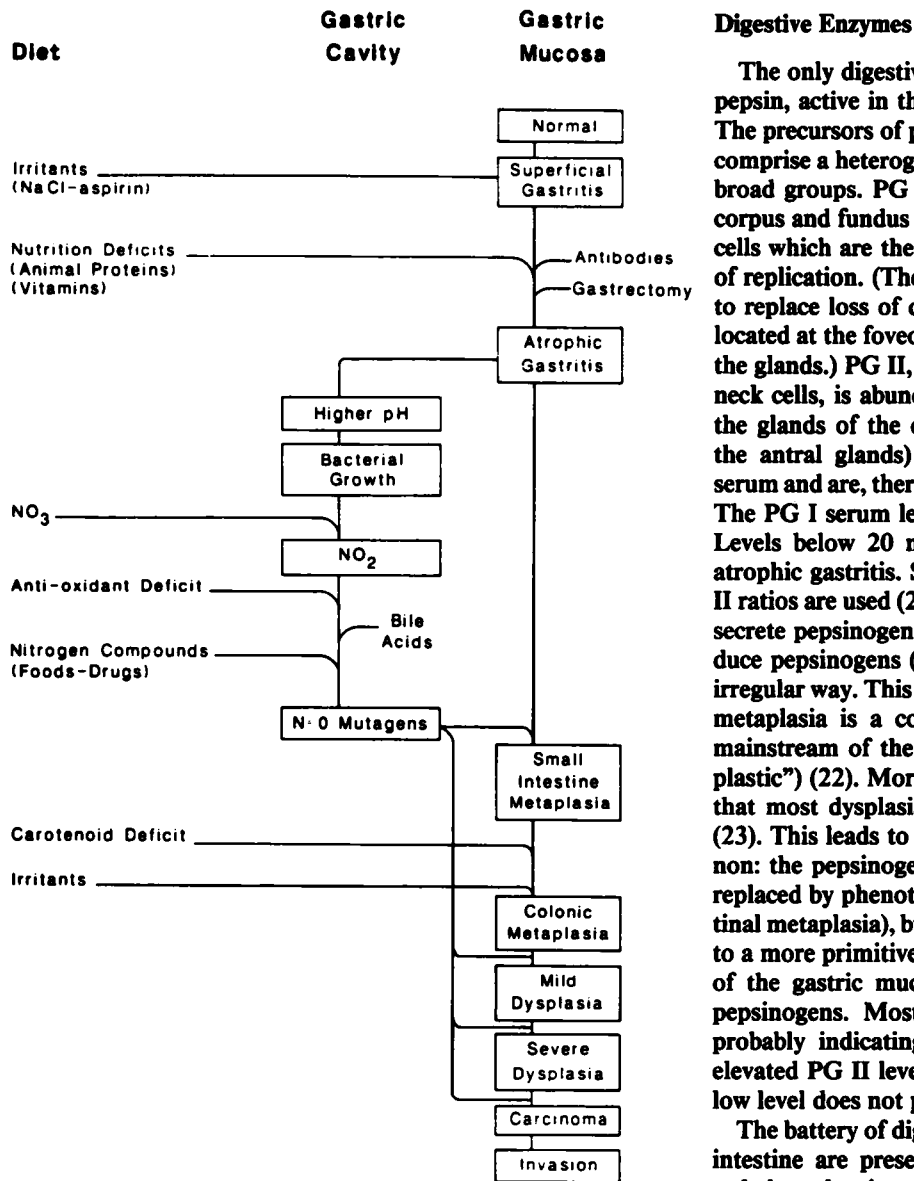


Fig. 1. Hypothesis of gastric cancer etiology.

this purpose and that small carcinomas arise in the metaplastic epithelium (14, 15). The prevalence of chronic atrophic gastritis and intestinal metaplasia correlates very well with the incidence of gastric carcinoma in interpopulation comparisons (16).

It has been recognized that intestinal metaplasia also represents a dynamic, apparently progressive, series of changes. In situations where the risk of cancer is low (young individuals, absence of dysplasia) the metaplastic mucosa resembles the small intestine ("small intestinal metaplasia"). In high-risk situations (older individuals, presence of dysplasia, or early carcinomatous changes) the epithelium resembles the large intestine ("colonic metaplasia"). Small intestinal metaplasia forms pseudo-villi or glands lined by absorptive eosinophilic enterocytes displaying a prominent brush border, alternating with goblet cells. Colonic metaplasia forms crypt-like structures lined by columnar cells devoid of a brush border, with abundant cytoplasmic mucin droplets of different sizes (17, 18). These two varieties of metaplasia are considered prototypes; intermediate steps are commonly observed, suggesting that a gradual transition from one type to the other is the rule. The transition is better examined with studies of digestive enzymes, mucin histochemistry, and antigen expression.

Digestive Enzymes

The only digestive enzyme present in the normal stomach is pepsin, active in the initial stages of the digestion of proteins. The precursors of pepsin (zymogen) are the pepsinogens which comprise a heterogeneous group of proteins which fall into two broad groups. PG I² is found mainly in the chief cells of the corpus and fundus mucosa and to a lesser degree in the "neck" cells which are the only normal gastric epithelial cells capable of replication. (The neck cells are multipotential and replicate to replace loss of differentiated cells which produce mucins if located at the foveolar surface, or pepsinogen if located deep in the glands.) PG II, although weakly stainable in chief cells and neck cells, is abundant in the antral ("pyloric") glands and in the glands of the cardiac mucosa (morphologically similar to the antral glands) (19, 20). Pepsinogens are present in the serum and are, therefore, excellent markers of atrophic gastritis. The PG I serum level reflects the degree of loss of chief cells. Levels below 20 ng/ml are highly correlated with extensive atrophic gastritis. Similar results are obtained when PG I/PG II ratios are used (21). Intestinal metaplasia cells usually do not secrete pepsinogens but dysplasia and carcinoma cells do produce pepsinogens (mostly PG II), although in a "patchy" and irregular way. This may be taken as an indication that intestinal metaplasia is a collateral phenomenon which is not in the mainstream of the genomic precancerous changes ("paraneoplastic") (22). Morphological observations, however, postulate that most dysplasias originate in previously metaplastic cells (23). This leads to an alternative explanation of the phenomenon: the pepsinogens disappear when normal gastric cells are replaced by phenotypically mature intestinal cells (small intestinal metaplasia), but reappear when the phenotype reverts back to a more primitive (dysplastic) cell, equivalent to the neck cell of the gastric mucosa which has the capacity to synthesize pepsinogens. Most PG-positive carcinomas express PG II, probably indicating some relationship to antral glands. An elevated PG II level may be indicative of gastric cancer, but a low level does not preclude such diagnoses.

The battery of digestive enzymes normally found in the small intestine are present in small intestinal metaplasia: sucrase, trehalase, leucine aminopeptidase, and alkaline phosphatase. This fact has been well documented in humans and has given rise to the denomination of "complete" to this variety of metaplasia. Most of those enzymes are missing in colonic ("incomplete") metaplasia, frequently accompanied by dysplasia or small carcinomas in other areas of the gastric mucosa (24-26). When comparing well advanced with less advanced metaplasia, the impression is gained that some enzymes disappear early in the process (*i.e.*, sucrase) while others are found in advanced cases, even if in small amounts (leucine aminopeptidase). There is, however, no constant relationship between the type of mucins secreted and the expression of specific digestive enzymes.

The abnormal presence of β -glucuronidase and lactic dehydrogenase in the fasting gastric juice has been observed in cases of carcinoma and in cases of sulfomucin containing (colonic) intestinal metaplasia, but not in atrophic gastritis (without metaplasia), or in metaplasia of small intestinal type (27, 28).

Mucins

The complexities of gastrointestinal mucin histochemistry have been recently somewhat simplified by the application of histochemical techniques which distinguish three basic proto-

² The abbreviations used are: PG I, pepsinogen I; PG II, pepsinogen II.

types of mucin. Neutral mucins, stained with the periodic acid-Schiff reagent, are normally present only in the foveolar cells and antral glands. Acid mucins are of two main types: (a) sialomucins which stain blue with the high-iron diamine Alcian blue stain and are normally present in the small intestine and the proximal large intestine; (b) sulfated mucins which stain dark brown with the high-iron diamine Alcian blue technique and are normally present only in the large intestine, more prominently in the distal colon and in the rectum. Other stains identify mucins which do not fall in these three main categories, such as sulfated mucins which do not stain with high-iron diamine (29). In the metaplastic process it appears that neutral mucins are gradually replaced by acid mucins and as the process becomes more extensive (more "advanced"), iron diamine-positive sulfomucins make their appearance. The latter become abundant when dysplasia or small carcinomas are present (30–34). It can then be proposed that the phenotype of metaplastic cells changes as follows: the gradual disappearance of neutral mucins is replaced first exclusively by sialomucins, followed by the predominance of sialomucins over sulfomucins, and ultimately by the predominance of iron diamine-positive sulfomucins. Most investigators agree that the presence of sulfomucins is associated with more advanced stages, including dysplasia and neoplasia. Sulfomucins, therefore, may be a useful marker of preneoplasia. Based on morphology and mucin histochemistry the metaplastic lesions have been divided into three types: type I expresses only sialomucins; type II expresses mixtures of sialomucins with neutral mucins or sulfomucins; and type III expresses predominantly sulfomucins (31).

Neutral mucins are also seen occasionally in gastric carcinoma cells which also may express sialomucins and/or sulfomucins in a patchy or irregular (clonal?) way. Since the same cells may occasionally express pepsinogens, it follows that the cancer cell is an anarchic entity which may express phenotypes of totally different mature cells: neutral mucin-secreting foveolar cells, acid mucin-secreting intestinal cells, and pepsinogen-secreting cells which could represent antral glands or chief cells. There is, however, one normal gastric cell type capable of expressing the same phenotype, although in a "weak" and patchy way: the neck cell. The mucin histochemical findings, therefore, reinforce the argument put forward in the discussion of pepsinogens: in the process of carcinogenesis in humans the normal gastric cells are replaced by cells expressing mature intestinal phenotype and these are then replaced by cells with immature phenotypes capable of synthesizing the same cytoplasmic products of the (multipotential) neck cells. It is not clear if the neck cell acts as a stem cell or if it is derived from a precursor stem cell. This multipotential cell was considered to give rise to gastric carcinomas, given their capacity to express phenotypic markers of several differentiated cells (29, 35). This interpretation implies that the role of the precancerous process is to awake dormant stem cells. The fact that the changes are gradual and increasingly regressive suggests instead the activation of dormant potentials (repressed genes?) within the already transformed cells which precede the final evolution to neoplastic cells.

Antigens

Linking the expression of gastrointestinal antigens to gastric carcinogenesis in humans is not a recent idea. Polyclonal antibodies produced with human colon and normal adult rat stomachs were found to bind to normal human fetal stomach; the intestinal component disappears soon after birth but reappears

in metaplasia and neoplasia. The gastric antigen persisted throughout adult life but showed a tendency to be depleted when metaplasia and neoplasia made their appearance. This led to the following statement: "The loss of adult and reemergence of fetal antigen in both metaplasia and neoplasia suggest a possible fundamental relationship between these conditions; the phenotypic variation may reflect cytogenetic liability, which has malignant transformation as a final irreversible step" (36). Many lines of research, focusing on specific groups of antigens, tend to give credence to the above assertion.

Blood group-related antigens have been "mapped" in the gastrointestinal mucosa (37, 38) and special attention has been given to Lewis^x, which is present in the normal fetal stomach but absent in the normal adult stomach. Monoclonal antibodies against Lewis^x have been detected in the serum of patients with gastric carcinoma (39, 40). The prevalence of such antibodies in the antral mucosa in gastric biopsies has been reported as follows: normal, 0% (0 of 37); grade 1 atrophy, 18% (2 of 11); grade 2 atrophy, 31% (5 of 16); grade 3 atrophy (intestinal metaplasia), 61% (8 of 13); grade 4 atrophy (advanced metaplasia), 100% (3 of 3) (40). The pattern reflects a gradual increase of the fetal antigen expression as the precancerous process advances.

Mucus-associated antigens have been detected in gastric cancer and intestinalized gastric mucosa (41–43). Three main antigenic groups associated with goblet cells have been described. M3SI (small intestine) and M3D (duodenum) have been observed in intestinal metaplasia of "benign" gastric mucosa. M3C (colon) as well as M3D and M3SI were found in metaplasia adjacent to gastric carcinomas. The latter pattern is similar to fetal duodenum which led us to postulate that as metaplasia advances, although it resembles colonic mucosa on morphological grounds, it may really be expressing the phenotype of fetal duodenum (42).

Other well known embryonal antigens have been detected in gastric carcinomas as well as in intestinal metaplasia and dysplasia. Such is the case of carcinoembryonic antigen (44) and α -feto protein (45). Carcinoembryonic antigen can be recovered from the gastric juice; in stomachs with minor histological abnormalities Nitti *et al.* reported levels below 100 ng/ml, while in metaplasia and gastric cancer it ranged between 224 and 3120 ng/ml (44). In addition to the above, other antigens are shared by cancer cells and intestinalized cells surrounding the tumor. Such is the case for pregnancy-specific β -glycoprotein (SP-1) and human placental lactogen. Metaplastic cells not associated with cancer do not express these antigens, but the two types of metaplasias with contrasting antigen expressions are not distinguishable on morphological grounds alone (46). Human chorionic gonadotrophin, present in normal neck cells, becomes abundantly expressed in metaplasia and carcinoma (47).

A murine fibrosarcoma-associated antigen which is expressed in fetal but not adult gastrointestinal tissue was studied in conjunction with [³H]thymidine labeling in gastric mucosal biopsies showing chronic atrophic gastritis and intestinal metaplasia. There was a remarkable coincidence between the increased thymidine labeling and the expression of the fetal antigens. Very few studies have been made in which two separate markers of premalignant changes are observed in the same cell compartments. In these experiments synchrony between the two phenotypic changes is apparent (48). A human second trimester fetal antigen has been found increasingly expressed as the precancerous process advances: 10% in superficial gas-

Table 1 Markers of differentiation

Morphology	Mucins			Pepsinogens		Intestinal enzymes			Antigens						Oncogenes	
	Neutral	Sialo	Sulfo	I	II	AP ^a	T-S	LAP	Le ^a	M3SI	M3D	M3C	CEA-aFP	PA	ras	c-myc
Normal	+			+	+											
Superficial gastritis	+			+	+											
Chronic atrophic gastritis	+			±	+				±					±		
Intestinal metaplasia																
Small intestinal type	±	+					+	+	+	+	+				+	+
Colonic type		±	+					±	+	+	+	+	±	±	+	+
Dysplasia					±								+	+		
Carcinoma	±	±	±		±				±				+	+	+	+

^a AP, alkaline phosphatase; S, sucrase; T, trehalase; LAP, Leucine aminopeptidase; Le^a, Lewis^a antigen; CEA, carcinoembryonic antigen; aFP, α -fetoprotein; PA, placental antigens; M3SI, small intestinal; M3D, duodenal; M3C, colonic.

tritis, 38% in chronic atrophic gastritis, 50% in intestinal metaplasia, and 86% in dysplasia (49).

Oncogene Expression

A few studies have shown that foci of intestinal metaplasia of the gastric mucosa express oncogene products. Noguchi *et al.* have reported elevated *M*_r 21,000 *ras* oncogene product in metaplastic cells (50). Ciclitira *et al.* (51) reported increased expression of the *M*_r 62,000 product of the *c-myc* oncogene in inflammatory, metaplastic, and dysplastic gastric mucosa. Some expression was also found in the epithelial cells of the mucus neck region.

Other Markers

Several other laboratory techniques can be applied to study the suspected progressive loss of differentiation: cytoplasmic products such as keratins, cytoskeleton alterations, and [³H]-thymidine incorporation, to mention some of them. Their further exploration in human material may throw additional light on the precancerous process. Ultrastructural studies have revealed cilia and branching microvilli in the cystically dilated basal portions of metaplastic glands, suggesting errors of differentiation rather than mutations (52, 53).

Most investigators agree that the gastric preneoplastic process manifests itself in humans not as an "all or none" phenomenon but as a gradual transition from the mature to the embryonal phenotype. This lack of "instancy" in the phenotypic change may be a problem when classifying metaplasia as a mutation. Repression and activation of specific genes may be a better hypothetical accommodation to the observations available in humans.

When the different compounds of the phenotype are studied (architecture, nuclear morphology, enzymes, mucins, antigen expression, etc.), synchrony is found only in the most general sense (Table 1). In most advanced cases in which dysplastic or neoplastic changes are found in some area of the mucosa, the metaplastic changes are extensive, the architecture resembles the colonic mucosa, the digestive enzymes are absent, sulfomucin is present, and embryonal or fetal antigens are expressed. But when "synchrony" is looked for in more refined steps, many unexpected results are obtained: the loss of digestive enzymes is somewhat irregular and does not always match the architectural or mucin findings; sulfomucins are occasionally found in small intestinal morphology; mature and "immature" antigens may be found in advanced dysplasia, etc. It is entirely possible that the genetic makeup of the subject and the intensity or frequency of the individual components of environmental

insults determine the pattern of phenotype changes. This area deserves further scientific exploration.

Modulation

The postulated gradual process from normal to neoplastic cells appears to take place in humans over an interval of many years. The forces which determine the progression (or lack of it) in this chain of events are poorly understood but appear to fall into different categories briefly discussed below.

Carcinogens. The model under study calls for the presence of genotoxic agents which induce successive cellular transformations. The possibility that these are *N*-nitroso compounds formed in the human stomach by nitrosation of locally available nitrogen-containing products has been extensively discussed (54, 55). One of the difficulties with this hypothesis has been that nitrosation of some amines (like proline, known to occur in humans) is most efficient at low pH while the supposedly precancerous stomach displays higher pH (56). Some recent observations, however, suggest that the proline model may not be the best indicator of cancer risk in humans. Bacteria cultured from previously operated stomachs (a well-documented precancerous condition) catalyze the nitrosation of morpholine to form *N*-nitrosomorpholine (a known carcinogen) at neutral pH and 37°C (57). Studies of the nitrosation of foods common in high-risk populations point in the direction of *N*-nitroso indoles as potential human carcinogens. Highly mutagenic *N*-nitroso indoles have been detected in nitrosated fava beans (58), as well as in Chinese cabbage and soy sauce (59), frequent dietary items in high-risk populations of Colombia and Japan.

Irritants. Epidemiological observations have linked certain irritants to higher gastric cancer risk, most notably excessively salted foods (60–62). Experimental evidence supports this contention. Highly salted rice diets lead to gastric atrophy in mice (6). Adding salt and/or other irritants such as aspirin to the diet of *N*-methyl-*N'*-nitro-*N*-nitrosoguanidine-treated rats, potentiates the effect of this carcinogen (10, 11, 63, 64). NaCl-induced damage of the gastric mucosa leads to increased DNA synthesis (65) and induces ornithine decarboxylase, an effect usually found with promoters of carcinogenesis (66). Salt intake is strongly associated with intestinal metaplasia (67).

Bacterial Infections. Pathogenic bacteria may play a role in the carcinogenic process. It has recently been realized that *Campylobacter pylori* is frequently associated with chronic gastritis (68). The infection is very prevalent throughout the world, but it approaches 100% in populations at high gastric cancer risk.³ Although the role of *C. pylori* is by no means understood, it appears that it may be an additional cause of gastritis and as

³ C. Cuello, personal communication.

such may participate in the precancerous process.

Protective Agents. Extensive epidemiological and experimental evidence indicates that certain substances act as protectors by creating obstacles to the process of gastric carcinogenesis. Some of those substances are micronutrients but most probably nonnutrient protective substances are normal components of the diet of many populations (69). Fresh fruits and vegetables as well as vitamin C appear to play such a protective role in case-control studies of chronic atrophic gastritis and intestinal metaplasia. Low blood levels of carotenoids and tocopherols have been found in patients with gastric dysplasias but not in patients with less severe lesions of the gastric mucosa, suggesting that if there is a causal association between these micronutrients and the gastric carcinogenic process, such association takes place only in the late stages of the process (12). Such speculation is supported by the studies of Santamaria *et al.* (70) in which carotenoids decreased the incidence of gastric carcinoma but not of the earlier stages of the carcinogenic process in rats receiving *N*-methyl-*N'*-nitro-*N*-nitrosoguanidine.

Genetic Susceptibility. Studies of native and migrant Japanese have shown that the reduction in the risk of gastric cancer (intestinal type) associated with migration to Hawaii is due to a delay of approximately 15 years in the start of the slope of the age-specific incidence curve. Once started the incidence curve of the migrants follows the same slope of that of the natives. This apparently indicates that the genetic susceptibility persists after migration, but the initiation of the carcinogenic process is delayed in the Hawaiian environment (71). Blood group A is more prevalent in subjects with diffuse type of gastric carcinoma than in the general population, which again points to a poorly understood genetically mediated susceptibility to gastric cancer (71). Segregation analysis of chronic multifocal atrophic gastritis in Colombia has shown Mendelian transmission of a recessive autosomal gene whose penetrance depends on age and on having an affected mother (72). The gene is very prevalent in the population studied: homozygous recessives account for an estimated 61% of the sampled population and have a penetrance reaching 72% at age 30 if the mother is affected and 41% if the mother is not affected. This interaction of genetic and environmental factors goes a long way toward explaining the contrasting incidence of the disease in different populations, the migration effects, and the time trends of gastric cancer incidence. The genetic susceptibility of the diffuse corporal gastritis associated with pernicious anemia (a totally different entity) follows a pattern of autosomal dominant Mendelian transmission (73).

Epilogue

Some lessons and inspirations for future research may be considered after a review of the gastric carcinogenesis model in humans.

The number of steps, the time involved, and the diversity of etiological factors which seem to play a role speak of a much greater complexity than that of the usual initiator-promoter experimental model. There seem to be prerequisites for specific steps and specific etiological factors. Negative epidemiological or experimental findings should, therefore, not be taken as negation of the role of a specific factor. A factor may be involved in the causation, but the wrong sequence of presentation or the absence of a prerequisite lesion may make it appear unrelated to causation. Epidemiological techniques may need to be used to address specifically the possible sequence of events and the preexistence of certain lesions. Etiological research provides

the opportunity to test specific factors against specific precursor lesions (testing segments of the model).

The same general path may be valid even in the presence of interpopulation differences; the specific carcinogen or carcinogens may differ between populations because the original precursor of the carcinogen may differ (*i.e.*, nitrosation of fish *versus* vegetables) (58, 74). The specific protectors may also differ (*i.e.*, food additives *versus* natural protectors in food).

The multitude of phenotypic changes observed in the precancerous process, and their apparently gradual occurrence, revive old comparisons with "stem" cells and their possible role in giving rise to cancer cells. It does appear that these multipotential cells are not "awakened" by other cells of the gastric epithelium but rather that gradual changes take place in epithelial cells which make them express phenotypes peculiar of stem cells. Whether these phenomena represent structural or functional changes in cellular DNA constitutes an interesting scientific challenge. There is a need to better define the synchrony, interrelations, and relevance of the different phenotypic changes. The abundance and variety of markers of loss of differentiation open new avenues for intervention via chemoprevention or dietary prevention.

Other models for human carcinogenesis may be developed, some of which may have similarities to the one just explored. To mention just a few, the following situations may be explored: (a) many similarities between esophageal and gastric carcinogenesis exist in spite of marked geographic differences in incidence, implying similarities in some segment(s) of the preneoplastic process; (b) oral, laryngeal, and esophageal cancers may be related to carcinogens which could be either delivered or synthesized *in situ* (*i.e.*, nitrosation of nicotine metabolites by salivary NO₂) (75) and modulators which may depend on specific tissue deficiencies of nutrients (not necessarily evident in blood levels); (c) nitrosation and dietary modulation may be involved in carcinogenesis of internal organs such as the lung and the pancreas (76). In summary, the time to explore more extensively human models of carcinogenesis may have arrived.

Acknowledgments

The development of the model described represents the work of a multidisciplinary team in which William Haenszel, Steven Tannenbaum, Martin Lipkin, and Carlos Cuello played prominent roles. My deep appreciation goes to them for their scientific contributions. Many thanks to Grant Stemmermann for his valuable suggestions concerning the manuscript.

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