The "minor changes" comprised diffuse abnormalities thought to be secondary to hypertension or chronic pyelonephritis, and small cysts and calculi considered to be of no aetiological significance.

The polycystic renal disease, the hydronephrosis, and one of the two diagnoses of severe pyelonephritis were already known. The finding of generalised abnormalities thought to be secondary to hypertension or urxmia, was anticipated; considered relevant or possibly relevant to the nephrectomy and renal transplantation with a satisfactory outcome up to 3 years later (b.p. 170/100 mm. Hg). Only one of the renal abnormalities found and considered relevant or possibly relevant to the aetiology or management of the hypertension was unsuspected before pyelography was done.

The patient with known severe pyelonephritis, the patient with hydronephrosis, and the patient with polycystic kidney were on hypotensive drugs at follow-up, as was the man with the renal transplant. Dietary changes were also made as necessary. The patient found, unexpectedly, to have pyelonephritis (apparently confined to the right kidney) underwent nephrectomy and remained normotensive without drugs during the first postoperative year. However, by 3 years she again required methyldopa to maintain normal B.P. readings.

**Discussion**

In this small series, only one unsuspected renal abnormality of possible therapeutic importance was revealed amongst seventy-six I.V.P.s carried out solely as part of the inpatient investigation of hypertension. One of the urographic diagnoses led to nephrectomy which, while not abolishing the hypertension in the longer term, may have facilitated continued medical management.

Four other patients had urographic abnormalities probably relevant to their hypertension, but in each case there were clear indications of renal disease and I.V.P.s would have been undertaken on grounds other than hypertension per se.

Our findings are similar to those from the much larger Glasgow study; and, especially since the procedure is not entirely free from risk, they cast doubt on the advisability of including excretion urography in the routine investigation of hypertension. The indications for its use should, perhaps, be the same in hypertensive as in normotensive populations.

S. M. B. is in receipt of a clinical research grant from the East Anglian Regional Health Authority.

Requests for reprints should be addressed to D. W. E.

**REFERENCES**


**A MODEL FOR GASTRIC CANCER EPIDEMIOLOGY**

**Pelayo Correa**

*Department of Pathology, Louisiana State University Medical Center, 1542 Tulane Avenue, New Orleans, Louisiana 70112, U.S.A.*

**William Haenszel**

*Biometry Branch, National Cancer Institute, National Institutes of Health, Bethesda, Maryland 20014, U.S.A.*

**Carlos Cuello**

*Department of Pathology, School of Medicine, Universidad del Valle, Cali, Colombia*

**Steven Tannenbaum** **Michael Archer**

*Department of Nutrition and Food Science, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139, U.S.A.*

**Summary**

It is postulated that one major subtype of gastric carcinoma ("intestinal type") is the end-result of a series of mutations and cell transformation begun in the first decade of life. The mutation could be a nitroso compound synthesised in the upper gastrointestinal tract by the action of nitrite (i.e., from food or saliva) on naturally occurring nitrogen compounds. Under normal conditions these nitroso compounds do not reach the gastric epithelial cell, presumably because their synthesis is inhibited by antioxidants present in food or because of their inability to pass the mucous barrier. The barrier may be overcome by abrasives or irritants such as hard grains, food with high sodium-chloride concentration, or surfactants. Once the first mutation occurs, the glandular gastric epithelium is gradually changed to intestinal-type epithelium, the mucous barrier altered, and the pH elevated. Under these conditions, bacteria proliferate in the gastric cavity and facilitate the conversion of nitrates to nitrites, thereby increasing the nitrite pool and the probability of formation of mutagenic-carcinogenic nitroso compounds. This process of gastric atrophy and intestinal metaplasia goes on for 30 to 50 years until some of the individuals affected have the final mutation or cell transformation which allows the cell to become autonomous and invade other tissues.

This hypothesis is supported by studies of the pathology, the epidemiology, and the chemistry of the process.

**Pathology**

Two main types of gastric cancer have been described by comparative histological studies. 2,3 The type more influenced by the environmental factors, "epidemic", is histologically best represented by what Järvi and Lauren first called the "intestinal" type because it is formed by intestinal rather than gastric cells. 1 When the gastric-cancer risk is reduced in a population, the epidemic type accounts for most of the reduction. 2,4 The rise in age-specific incidence-rates of this type begins at older ages in low-risk communities and has a characteristic steep slope in
both high- and low-risk countries, the main difference between the two populations being a longer incubation period in the low-risk areas.4

The long incubation corresponds to the evolution in the gastric mucosa of precursor lesions—namely, chronic atrophic gastritis and its companion, intestinal metaplasia.3 The process begins as an inflammatory change with focal necrosis of the glandular necks leading to atrophy of the normal gastric mucosal epithelium and its gradual replacement by cells which are foreign to the stomach but occur normally in the intestine: goblet cells, absorptive cells, Paneth cells, and argentaffine cells.5 The process starts at the junction of the antrum and the body of the stomach as independent foci which then become confluent and spread first along the lesser curvature and then to other areas of the mucosa. The target organ is transformed into something like a chimera of intestinal mucosa and gastric muscle. A series of mutations from gastric to intestinal to atypical to invasive epithelial cells seem to take place.

### Epidemiology

Environmental factors play an overriding role in the aetiology of gastric cancer. The declining incidence-rate observed in recent decades is the most eloquent evidence of this assertion. The environmental factor may be a carcinogen in food. Correlations between certain food items and risk of gastric cancer have been found, but no food item can be identified which is common to all (or most) high-risk areas. More consistent results have been obtained for food items associated with a decreased risk such as lettuce and green, fresh, leafy vegetables.6 It seems, therefore, that the interaction of food items in the microenvironment of the stomach is a determinant of cancer risk. The opposing forces on the inductive side are mainly abrasive or irritant items such as fried foods or vegetables with hard cortex or items which have exceptionally high salt concentration (pickled vegetables, dried salted fish), presumably capable of breaking the mucous barrier.7 On the protective side, we have mainly fresh vegetables and citrus fruits, rich among other things in vitamin C.8 These food items, therefore, seem to condition the effectiveness of a carcinogen rather than being the carcinogen itself.

Zones of extremely high risk of stomach cancer have been identified in a mountainous rural region of Colombia (Narino), and a gastroscopic survey of population samples of apparently well individuals showed that those who have lived the first ten years of their lives in a “high-risk” environment had a greater prevalence of intestinal metaplasia. The difference diminished with age, indicating a delay in the initiation of the process. We also found that the risk of precursor lesions is increased by certain hard grains like corn and by local berries (moras) and decreased by lettuce.

### Chemistry

The mutations might be caused by exposure to a chemical mutagen-carcinogen, possibly an N-nitroso compound synthesised somewhere between the oral and gastric cavities from endogenous nitrite and the nitrogenous constituents in the food. Salivary nitrites are the result of reduction of nitrates by several species of bacteria. The level of nitrate ingested and types of bacteria present in the mouth (i.e., as a result of tooth decay) may influence the concentration of salivary nitrites. Nitrites appear in cultures of Staphylococcus epidermidis only after high concentrations of potassium nitrate (1000 p.p.m.) are added to the medium.9 Work in England, Chile, and Israel has implicated environmental levels of nitrate in gastric-cancer mortality.10 We have found high concentrations of nitrate (up to 80 p.p.m.) in the water supplies of towns in the south of Colombia where the gastric-cancer risk is extremely high. The urine of the dwellers of such towns also contains high concentrations of nitrate.

The nitrite content of such water supplies and urine samples is negligible. The possible role of salivary nitrite is being investigated. Intragastric nitrosamine synthesis and its potential carcinogenic role has been suggested.11 For example, methylguanidine (M.G.), a compound naturally present in several foods, is converted into a potent mutagen after exposure to sodium nitrite in both simulated and real human gastric juice.12 The final product of this reaction is methyl-nitrosourea (M.N.U.), a potent carcinogen. The potent mutagen M.N.G. (N-methyl-N'-nitro-N-nitrosoguanidine) is carcinogenic to the glandular stomach of a variety of rodents and dogs.13 Nitrosation of a number of naturally occurring guanidines produces compounds which have mutagenic activity. Similar activity has been shown for several arginine-containing peptides and for one aminoacid: L-arginine.14 Carcinomas of the oesophagus have been induced in mice and rats by simultaneous feeding of amines and nitrite.15 Surfactants facilitate absorption of M.N.G. from the glandular stomach. Formation of nitrosamines at neutral pH in the presence of bacteria has been demonstrated. Nitrosamines have also been shown to form under these conditions in intestinal contents and the infected bladder of the rat.16 We (S. T. and M. A.) have shown that the addition of secondary amines to human saliva produces nitrosamines at a greater rate than would be predicted by simple chemical kinetics. Living bacteria are involved in this process. In southern Colombia, we have shown that people with advanced intestinal metaplasia have gastric anacidity. This condition allows growth of microorganisms in the stomach which could then produce nitroso compounds from ingested nitrogen compounds and endogenous nitrite.

In conclusion, observations made independently in several countries can be construed as supporting the hypothesis outlined in our summary. Further work is needed to clarify some of the missing links. We believe that, if proven, this hypothesis offers hope for preventing the disease.

This work was supported by Public Health Service contracts NO1-CP-53521, NO1-CP-33315, and NO1-CP-33286.

### REFERENCES

2. Lauren, P. Ibid. 1965, 64, 31.

References continued overleaf
IMMUNOLOGICAL BASIS FOR LATENCY, RECURRENTS, AND PUTATIVE ONCOCENICITY OF HERPES SIMPLEX VIRUS

T. LEHNER  J. M. A. WILTON
E. J. SHILLITOE

Department of Oral Immunology and Microbiology,
Guy's Hospital Medical and Dental Schools,
London SE1 9RT

Summary

The development of latency and recurrent infection after primary herpes simplex virus (H.S.V.) infection can be interpreted in terms of cell-mediated and antibody responses to virus-specific antigens and Fc receptors on the surface of the infected cells. Primary infection will induce immune responses to the virus, and antibody cell-dependent cytotoxic mechanisms will kill most of the virus and virus-infected cells which are accessible to killer cells. H.S.V. will be sequestered to the nerves and will migrate centripetally along the axons to the trigeminal or sensory ganglia. Latency in the trigeminal ganglion may be mediated by IgG antibodies binding to both H.S.V. antigens and Fc receptors. Derepression of the viral genome may be induced by factors which weaken the binding of antibodies to the antigen and Fc receptor; the virus will replicate and migrate centrifugally along the axon, to be shed at the nerve endings. In the presence of some defect in T lymphocytes, acting at the neuroepithelial junction, a recurrent herpetic lesion will be precipitated. There is some evidence that H.S.V. may be associated with squamous-cell carcinoma, and it is postulated that the enhanced cell-mediated and antibody responses to H.S.V. may destroy cells containing the viral genome but allow the emergence of an oncogenic genome. Double binding of the Fc receptor and H.S.V. antigen by IgG antibodies or immune complexes on the surface of carcinoma cells may prevent killing and allow these cells to proliferate into invasive tumours.

INTRODUCTION

The relation between primary infection, latency, and recurrent infection by herpes simplex virus (H.S.V.) has been a subject of intensive investigation. During the past 3 years a large number of virological, immunological, histochemical, and clinical investigations have advanced our understanding sufficiently to justify a general hypothesis of the mode of transmission of H.S.V. in the tissues, resulting in latency and activation of H.S.V. to induce recurrent infection.

We suggest that the clinical or subclinical primary infection, resulting in latency and recurrent infection by H.S.V., can be interpreted in terms of the cell-mediated immune and antibody responses to H.S.V. and the expression of a virus-specific antigen and an Fc receptor on the infected cell surface. These criteria will be also applied to interpret the possible relationship between H.S.V. and squamous-cell carcinoma.

PRIMARY H.S.V. INFECTION

Surface Markers in H.S.V.-infected Cells

Within less than 6 hours the infected cell surface acquires a virus-specific glycoprotein antigen and an Fc receptor.2-4 These surface markers may play an essential part in the immune responses involved in cytotoxicity, latency, recurrent infection, and carcinoma.

Relation between Cellular and Antibody Responses

The immune responses in both guinea pigs, immunised with viable H.S.V. in Freund's complete adjuvant,5 and in rabbits injected with H.S.V.6 showed that cell-mediated immune responses precede the appearance of serum antibodies by 3-4 days. These results are difficult to compare with those found in man7 because there is no way of assessing the incubation period in primary infection in man. Nevertheless, the development of complement-fixing antibodies and lymphocyte transformation seem to have a similar time-course, but the production of macrophage migration-inhibition factor (M.I.F.) is delayed by 4-8 weeks. This was observed on sequential examination in five out of seven patients, but in the remaining two patients M.I.F. was not detected and both developed recurrent herpetic infections.

Serum Antibodies

IgG antibodies can be found in all infected individuals, but IgM or IgA antibodies are found in some and not in others.8 Serum antibodies reach their maximum titre within 3 weeks of primary infection, and IgM precedes IgG. Surprisingly, secretory 1S IgA antibodies in saliva or tears have not been identified, and these secretions carry IgG (or 7S IgA) class of antibodies to H.S.V.9

Immune Complexes

Incubation of H.S.V. with IgG or IgM class of antibodies results in immune complexes with little or no viral neutralisation and the immune complexes remain infectious, but the addition of complement neutralises 95% of H.S.V.10 However, others11 have not found complement to be necessary for neutralisation of H.S.V. Soluble viral antigen, nucleoproteins, and membrane antigens may be released from virus infected cells and these may combine with antibodies to form immune complexes. These may cause pathological changes by their deposition in vessel walls and induction of complement activation and the release of inflammatory factors.

Cell-mediated Immunity

Seropositive individuals give delayed hypersensitivity reactions to H.S.V.12 and in vitro sensitised lymphocytes from these individuals will undergo blast transformation and produce the following lymphokines: M.I.F., lymphotoxin, chemotactic factor, and interferon.13-16 In addition the lymphocytes are cytotoxic for H.S.V.-infected target cells.17,18 There is also good evidence that T lymphocytes are involved in at least some of these functions.17,18 In primary H.S.V. infection in man lymphocytes are sensitised within the incubation period, but paradoxically the T cells are impaired during the initial phase of virus infection.7 Since lymphocyte transformation to H.S.V. in healthy individuals is predominantly a function of T lymphocytes, it is likely that during infection the virus might affect specifically T lymphocytes, thereby causing a transient cell-mediated immunodeficiency and permitting the