Three decades of gastroenterology in Soweto South Africa: from descriptive to scientific observations

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Chapter 1

Co-ordinating document

Selected list of publications

Scope of thesis
The publications are presented under the following sections:

B. Intestinal diseases conundrum.
C. Studies on acute and chronic pancreatitis
D. Helicobacter pylori enigmas

This section comprises 21 publications (Page 7-8). The studies focus on disorders of the oesophagus, stomach, duodenum, small and large intestine and biliary system. 6 publications on the urban experience are included. The articles describe the disease patterns and emergence of Western chronic digestive diseases in the urban Black. In addition, occurrences, characteristics, clinical manifestations and aetiological associations of the above disorders are discussed. This section forms a database for the development of the thesis.

B. Intestinal disease conundrum
In Soweto non-infectious large bowel diseases have very low incidences despite changes in life style, dietary and non-dietary (page 7 - 8). Risk factors favouring an increase in bowel diseases include Westernization of diet with a decreasing intake of fibre containing foods, and changes in bowel function. Thus stool weights, defecation frequencies, oro-caecal transit times and whole gut transit times in Sowetans approximate those of Western populations. Factors believed to be inhibiting a rise in bowel disease are physiological malabsorption of lactose, maize, fructose. Sucrase activity is significantly lower compared with Whites. There are also differences in colon cell proliferation, faecal short chain fatty acids, faecal pH and colonic microflora compared to White groups.
A hypothesis to explain the persistent low prevalence of Western digestive diseases in Africa has been proposed. It is suggested that the critical events which occur in early infancy lay the foundations for a healthy gastrointestinal tract which can withstand insults that may occur in later life. Central to this hypothesis is the quality of the intestinal bacteria, the integrity of the
immune system, and dietary factors in early childhood. This combination of factors may explain the paucity of Western digestive diseases in African adults, despite the rising prevalence of factors propitious for their increase.

The conundrum and hypothesis are discussed in publications at page 9 and 10.

C. Studies on acute and chronic pancreatitis
Pancreatitis was a rare disease among Sowetans until the 1970's when the emergence of the disease was first recorded. It has since become a common clinical entity and both acute and chronic pancreatitis now appear to be endemic at Soweto and carry a substantial toll in terms of morbidity and mortality.

Alcohol excess is the obvious aetiological factor, but several observations question traditional interpretations on its modus operandi. Other factors may play an important role in the development of the disease.

The 'oxidant stress' hypothesis developed by Braganza (the Manchester hypothesis) is in accord with this notion. The hypothesis envisages oxidant stress in pancreatic acinar cells as the initiator of pancreatic injury in non-gallstone acute pancreatitis and in chronic pancreatitis.

The emergence of chronic pancreatitis, clinical characteristics of acute and chronic pancreatitis and screening for chronic pancreatitis, and discussed in this thesis (page 10–11).

Evidence substantiating the 'oxidant stress' hypothesis in Sowetans is presented in publications at page 11.

D. Helicobacter pylori enigmas
Helicobacter pylori is ubiquitous in Africa with acquisition in childhood the rule. Despite the prevalence of a virulent strain (in Soweto most H.pylori organisms were Cag A and VacAS₁ (positive) H.pylori associated pathology (duodenal ulcer, gastric ulcer and gastric cancer) has a variable often low distribution in sub-Saharan Africa which does not parallel its prevalence in the population.
In many Africans H.pylori seems to have a different natural history than in developed countries. It has been shown that the progression to atrophic gastritis in Africa does not differ from that reported in other regions, but that yet unidentified factors may play a role in inhibiting progression to gastric cancer. Moreover, studies have suggested that the specific IgG subclass response to H.pylori was a predominately IgG1 (suggestive of a Th2 response). The Th2 response may provide a protective effect against development of gastric cancer. It is suggested that host immune mechanisms may be the key to different responses to H.pylori in the developed and developing world. H.pylori enigmas are discussed in this the publications at page 11 and 12.
Selected List of Publication

A. Database digestive diseases in Soweto:

Oesophagus

Stomach and Duodenum

Large Intestine (Descriptive)

Appendicitis

Diverticular Disease

Inflammatory Bowel Disease
Colorectal Polyps and Cancer

Nutrition

Gallstones

Tuberculosis and Amoebiasis

The Urban Experience
B. Intestinal disease conundrum

Small Intestine

Large Intestine (Physiology and Hypotheses)

C. Studies on acute and chronic pancreatitis

Emergence and genesis of chronic pancreatitis

Clinical characteristics of acute and chronic pancreatitis

Screening for chronic pancreatitis

Studies on the aetiology of pancreatitis


D. Helicobacter Pylori enigmas


Scope of Thesis

Database digestive diseases in Soweto

Anecdotal evidence suggested that diseases of lifestyle were uncommon among Sowetans. However, there was sparse published information with regard to digestive diseases in Africans. A data base to identify the pattern of disease was thus essential. Analysis of the data confirmed that most Western, digestive diseases were uncommon or rare. In the upper gastrointestinal tract hiatus hernia, reflux oesophagitis and gastric ulcer were uncommon (publications 2, 4). The large intestine in the vast majority of Blacks is conspicuous by the rarity of colorectal adenomas and the uncommonness of colorectal cancer, diverticular disease, Crohn's disease and ulcerative colitis. Appendicitis although more common, is still only one-tenth that of Johannesburg Whites (publications 5 - 10).

Examination of the data revealed three diseases which differed from the above pattern - squamous cancer of the oesophagus, duodenal ulcers and pancreatitis (publications 1, 4, 37). Notional concepts deduced from this evidence raised questions. Why are Western diseases uncommon and which factors distinguished the three more common diseases?

In order to understand the questions raised an explanation and formulation of new ideas and concepts was required.

Background

Urbanisation and industrialisation change social patterns which impact on diseases of life style. Soweto has a continuing influx of rural Black people who merge into and contribute towards an ever-growing permanently urbanised population. The Black immigrant leaves a rural tribal socio-cultural milieu for the multi-ethnic Western environment of the city. He moves from a subsistence economy into one requiring new skills, new concepts of time, work attitudes and different kinds of work relationships. He is, in addition removed from the closeness of a rural community to the anonymity of city life where his residential
arrangements, family life and physical environment are very different from those which existed in the countryside (publication 17).

This schism results in a tenuous attempt to preserve some aspects of traditional culture, which is reflected in the attempt of the urban Black to retain vestiges of traditional healing.

**Complications of traditional healer practices**

Most of the population of Soweto consults initially with a traditional healer, before seeking assistance of Western medicine. For effecting a cure, the traditional healer uses enemas and emetics more commonly than other forms of treatment. They are used for various reasons including ritual purposes; as an aperient, aphrodisiac or emetic; and for the treatment of impotence, gastrointestinal disturbances and dysmenorrhea. In the city, use and abuse of emetics and enemas can result in damage to almost the entire gastrointestinal tract.

In particular, the use of enemas containing substances such as vinegar, soap, caustics, chloroxylenol, potassium dichromate, copper sulphate, potassium permanganate and brown sugar can result in ritual-induced enema colitis. Peritonitis and rectal bleeding are the clinical hallmarks of this condition.

It may be thought paradoxical that urban people should accord such respect to what in Western terms may seem an anachronism. The belief in mysticism is, however, an integral element of African culture and is fostered in the urban situation by the traditional healer (publications 19-21).

**Changes in alcohol consumption pattern**

In traditional African society, drinking of a low alcohol (+ 3%), sorghum based beer was part of the social fabric. The impact of urbanisation on alcohol consumption is reflected in the change in drinking patterns of the South African Black population in general, in Soweto in particular (publication 37).

During the past 50 years, the consumption of Western type spirits and beers in Soweto and other major South Africa cities has to a large extent replaced traditional home brews.
Prior to 1962 legislation forbade the sale of Western type liquor to the Black population. This legislation was subsequently repealed and resulted in a radical change of drinking habits. Evidence for this change is that prior to 1962 iron overload was common in adult Black males of Southern Africa where the majority of adults showed varying degrees of tissue siderosis. In 1950 Walker and Arvidsson demonstrated that the excess iron was due mainly to the uptake of the element from iron utensils used during the preparation of fermented alcoholic beverages.

There has been a reduction in both the prevalence and severity of iron overload in urban South African Black men over the past 50 years. This can be ascribed to several changes in drinking habits. The new legislative directive was the most important reason for the change in drinking habits. This has resulted in an increase in the consumption of spirits, notably brandy and fortified wine and beers, with a corresponding decrease in the consumption of home brewed traditional beverages.

Additional evidence for the change in drinking habits in Blacks is the alteration in the manifestation of liver disease. Micronodular cirrhosis associated with iron overload is characterised by the presence of large quantities of haemosiderin and there is no fatty change, alcohol hepatitis, alcohol hyalin or alcoholic cirrhosis. This contrasts with the presentation of micronodular cirrhosis observed in Western societies after prolonged consumption of spirits. Micronodular cirrhosis with fatty change, alcoholic hyalin, alcoholic hepatitis and alcoholic cirrhosis has now appeared in the Black population.

It is significant that 15 years after Western type alcohol was made available, alcohol-induced chronic calcific pancreatitis (CCP) began to be diagnosed in Soweto. Observations over a 3-year period (1981-1983) on 55 patients show that it has devastating effects in terms of morbidity with a high incidence of complications and a mortality of 15%. CCP affects mainly young men (mean age 40 years) and develops approximately 16 years after the commencement of drinking alcohol. The disease has a high morbidity with complications including diabetes, obstructive jaundice and pulmonary tuberculosis. Possible reasons for the high morbidity rate are that diagnosis is usually made at an advanced stage of the disease, most patients do not stop drinking and compliance with treatment is poor (publication 37).
Changes in the content of traditional brews

Paradoxically, in areas where traditional brews are still consumed, the replacement of the nutritious sorghum by 'vitamin' deficient maize, in the brewing of beer, is cited as one of the major reasons for the epidemic of squamous oesophageal cancer in certain regions of Africa. Cook (1975), proposed a hypothesis that both the geographical and temporal distribution of oesophageal cancer in Africa could reflect the use of maize as a major ingredient of alcoholic drinks. The traditional beer is made from malted sorghum and a starchy adjunct - a sorghum grain or maize (com)\(^5\). In fact maize has been an ingredient of beer even before the turn of the century, but the percentage of maize used in beer has increased considerably in recent times\(^5\)-\(^7\). The use of maize instead of sorghum grain has resulted in a decrease in thiamine, niacin and riboflavin of traditional brews\(^8\). This would have dramatic effects on the B vitamin status of people, such as the oesophageal cancer patients, who consume large quantities of beer and whose low socio-economic status will result in a generally poor diet that is largely composed of maize (publication 1). From his studies in the Transkei, Van Rensburg\(^9\), has concluded that 'the dominant and unifying factor in the aetiology seems to be the nutritional status'. Most evidence suggests that a chronic low status of zinc, magnesium, riboflavin and nicotinic acid predisposes the oesophageal epithelium to cancer formation\(^9\)-\(^10\).

References
Intestinal disease conundrums

The paucity of non-infectious diseases prevails despite the presence of environmental factors which are propitious for their increase. In contrast, their incidence is high in Western populations, although they were very much lower at the turn of the last century. Urbanisation of Africans is accompanied by changes in environmental factors and lifestyles which either promote or inhibit increases in intestinal diseases (publications 32, 34, 35).

Factors favouring an increase in intestinal disease in Sowetans (publication 32)

Diet
In African countries, considerable changes in diet have occurred and are continuing, with falls in the intake of plant foods but rises in those of animal origin. In South Africa, among rural Africans a generation ago, of the total energy intake, protein supplied 10-11%, fat 15-20%, and carbohydrate 70-75%. Dietary fibre intake averaged 30-35g daily. In Johannesburg, a recent study showed that the proportions of nutrients supplying energy were protein 14%, fat 30%, and carbohydrates 55%. Mean total daily energy intake was 2150 kcal, with 82g of protein, 74g of fat, 250g of carbohydrate, and 14g of fibre. Maize meal (previously and still the case in many families) is the staple food but is being replaced by bread, mainly White bread. Consumption of fruit, vegetables, and meat is low because of their cost. Of major significance, the marked reduction in fibre intake and rise in fat consumption has been associated with a reduced intake of antioxidants. Simultaneously, however, approximately one tenth of urban Africans are now sufficiently better off to have a dietary intake and pattern approaching that of the White population.

Non-dietary changes
In recent generations of Western populations there has been a continuing reduction in physical activity at work, and in relation to transport and leisure. In Africans, physical activity
is falling considerably in urban dwellers. Additionally, smoking and alcohol consumption, particularly in men, are rising. The adverse effect of low physical activity is well known.

Bowel function
Stool weights, defaecation frequencies oro-cacccal transit time and whole-gut transit times in Sowetans approximate those of Westernized populations rather than those of rural Blacks. Mean colon transit time was shown to be similar in Sowetan and British men, although shorter in African women, compared with British women (publication 26).

Factors inhibiting an increase in intestinal diseases in Sowetans (publication 32)

Carbohydrate Malabsorption
Fermentation is one of the major physiological functions of the large bowel in which energy yielding substrates are broken down by anaerobic bacteria to yield short chain fatty acids, carbon dioxide, hydrogen and energy which the flora use for growth and maintenance of cellular function. The marked reduction in fibre intake means that a lower concentration of substrate should reach the colon thereby limiting fermentation. However the loss is compensated for by physiological malabsorption of various carbohydrates in Africans. These include maize, lactose and fructose (publications 22, 23, 25). Sucrose activity is significantly lowered compared with Whites but whether this leads to sucrose malabsorption is not yet known (publication 26).

Diet
Fat intake has increased with urbanization but is still well below fat consumption in Western societies. The Soweto study showed that fat supplied 24% of energy. The inference is that present day urban Blacks have been habituated to a fat intake much lower than that of prosperous Western populations. The intake of saturated fat was also low, with a mean of about 17g per day, and supplies about 9% of energy. The low intake of fat is compatible with relatively low mean serum cholesterol levels of urban Blacks (publication 27).

Cell proliferation
A study by Van't Hof et al (1995) (publication 31) from Johannesburg showed that White control subjects had a significantly higher mean total labelling index than African controls (phase II proliferative lesion). In addition, the proliferative pattern of the White controls
showed a comparatively large amount of dividing cells in compartment 2, compared with the African controls (phase I proliferative lesion). There was, however, a significant difference in age between White and Black controls. It is noteworthy that there was a trend towards a higher rate of cell proliferation with age in the White control group, although this was not significant.

**Faecal short chain fatty acids**

Mean values for all components of faecal short chain fatty acids (SCFA), except butyrate, were found to be significantly higher in Africans compared with White subjects (publication 29). The role of butyrate as a major energy fuel and control factor of cell proliferation has been established.

**Faecal pH values**

Faecal pH values are significantly lower in African adults and children compared with Whites (publication 28).

**Colonic microflora**

There is evidence that in Africa infants the bacterial flora are qualitatively different and produce significantly more short chain fatty acids, specifically butyrate than White children (publication 34, 35).

In the context of the above it is apparent that in South African Blacks inhibiting factors outweigh promotive factors for increases in intestinal diseases.

**Confounding aetiological factors in intestinal diseases**

Hypothesis (publication 35)

In the context of poverty in infancy, an adverse environmental situation conditions the gut and, paradoxically, acts as a protective factor against subsequent digestive diseases in adulthood.
Developing countries almost invariably are characterised by poor sanitation and housing, with overcrowding and lack of access to clean water. Rapid urbanisation is becoming in many regions of Africa, leading to marked changes in lifestyle - diet, decrease in physical activity but increases in smoking and alcohol consumption, all features of populations in transition.

However, despite some environmental factors which favour an increase in the incidence of Western degenerative diseases, the incidence remains low. We hypothesise that the critical events which occur in early infancy lay the foundations for a healthy gastrointestinal tract which can withstand insults that may occur in later life. Central to this hypothesis is: i) the quality of the intestinal bacteria; ii) the integrity of the immune system and iii) dietary factors in early childhood (publication 35).

i) Quality of intestinal bacteria. There is evidence that in African infants the bacterial flora are qualitatively different and produce significantly more short chain fatty acids, specifically butyrate, than White children\(^1\).

ii) Integrity of the immune system. With regard to the immunological reaction to previous infections, a study showed that mean immunoglobulin (IgG) levels in Johannesburg Africans was higher than that of their counterparts in developed populations. The immune response to H.pylori in Africans, which is consistent with a Th2 immune response is further evidence of immunological protection (publications 55, 55).

iii) Dietary factors in early childhood. Relatively low energy intake during early childhood inhibits tumorogenesis in later life. Most African children live in poor conditions and undernutrition is usual, as manifested by the high proportions (15-35%) who are less than the fifth centile of reference standards for growth. The staple diet of children is maize meal, which although relatively low in fibre, is high in resistant starch (publications 33 - 35). It is believed that this combination of the above factors may explain the paucity of Western digestive diseases in African adults, despite the rising prevalence of factors propitious for their increase.
Studies on acute and chronic pancreatitis

Acute and chronic pancreatitis are common diseases in Soweto and they cause considerable mortality and morbidity. The emergence of the disease can be tracked from the 1920's but the increased frequency began in the 1970's and parallels urbanisation and industrialisation at Soweto (publications 37, 38). Alcohol excess is the obvious aetiological factor, but several observations question traditional interpretations on its mode of action (publication 53).

The first attack of acute pancreatitis pursues an aggressive course so that within a year 40 percent of patients develop chronic pancreatitis (publication 39). Integral to the pathogenesis of pancreatitis is the oxidant stress hypothesis in which the acinar cell is the site of mounting oxidant stress usually as a result of exposure to xenobiotics that induce cytochrome P450 mono-oxygenases while depleting glutathione. Each burst of oxidant stress may disrupt exocytosis and trigger an attack of pancreatitis by interfering with the methionine-to-glutathione transsulphuration pathway, which interacts with ascorbate and selenium. As a result free radical oxidation products are diverted into the pancreatic interstitium, causing mast cells to degranulate and provoke inflammation activation of nociceptive axon reflexes and profibrotic interactions. In Sowetans the cascade is evoked not only by the exposure to xenobiotics but by the low intake of vitamin C (publication 53).

The similarity in free radical marker and antioxidant profiles in the pilot studies of acute pancreatitis and chronic pancreatitis at Soweto suggest that these two conditions may be part of a pathobiological spectrum, linked by gradations in acinar cell GSH status, with a greater degree of GSH depletion in chronic pancreatitis as a result of conjugating reactions with xenobiotic metabolites (publications 48, 49, 50). Further, asymptomatic chronic alcoholics had plasma glutathione concentrations that were midway between the values in non-alcoholic controls and patients with chronic pancreatitis being significantly different from each (publication 53). The studies also indicate that apparently healthy Sowetans were actually in a

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state of oxidant stress that was tied in with their very poor vitamin C status, and lower selenium concentrations that in the UK (publication 48).

A case control study identified two environmental factors in each disease, namely, heavy alcohol consumption and low intake of fruit (a major source of vitamin C). Parallel trends on blood biochemical analysis indicated heightened free radical activity coupled with poor antioxidant status (publication 47).

The clinical features of chronic pancreatitis indicate a high morbidity with a high frequency or pulmonary tuberculosis and diabetes mellitus diagnosed at initial presentation. A disquieting mortality rate of 15% over a 3 year period in one survey of chronic pancreatitis may be an underestimate because many patients are lost to follow up (publications 37, 38).

The most exciting outcome of the studies at Soweto, is that prophylaxis against chronic pancreatitis may be possible by the simple measure of a daily tablet of vitamin C, perhaps fortified with selenium. The protection conferred by these substances in experimental studies of alcoholic toxicity provides scientific support for this proposal (publications 48 - 50).

Helicobacter pylori – The African enigma

Helicobacter pylori is ubiquitous in Africa with acquisition in childhood the rule. Despite the prevalence of a virulent strain (in Soweto most H.pylori organisms were Cag A and VacAS\textsubscript{1} positive) H.pylori associated pathology (duodenal ulcer, gastric ulcer and gastric cancer) has a variable often low distribution in sub-Saharan Africa which does not parallel its prevalences in the population (publication 57).

The World Health Organisation has designated Helicobacter pylori as a class 1 (definite) carcinogen for gastric cancer. The situation in Africa has given rise to the term 'African enigma' - a high prevalence of H.pylori with a perceived low prevalence of gastric cancer\textsuperscript{1}. In many Africans H.pylori seems to have a different natural history than in developed countries. It has been shown that the progression to atrophic gastritis in Africans does not differ from that reported in other regions, but that yet unidentified factors may play a role in inhibiting progression to gastric cancer\textsuperscript{2}.

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Moreover, studies have shown that the specific IgG subclass response in Sowetans to H. pylori was a predominately IgG\(_1\) (suggestive of a Th2 response) whereas that in the Australian and German population was a predominately IgG\(_2\) subclass response (suggestive of a Th2 response). The Th2 response may provide a protective effect against development of gastric cancer (publication 56).

It is suggested that host immune mechanisms may be the key to different responses to H. pylori in the developed and developing world. Interestingly, in a study by Ally et al\(^3\), to determine the total IgE antibody levels (surrogate marker for parasitic infection) in Sowetan adults and children, they found a high percentage of subjects to have total IgE and total IgG\(_1/G_2\) levels above the normal range. These findings suggest that the prevalence of previous g.i.t. infection in Sowetans is high, a finding that may explain the different immune responses to H. pylori in this community.

The situation in Africa also highlights other current controversial issues. It has been suggested that H. pylori in most people is harmless and may have potential benefits. Indeed the organism may be protective against the development of gastroesophageal reflux and its complications. Data indicate that hiatus hernia, gastro-esophageal reflux, Barrett's oesophagus and adenocarcinoma of the oesophagus are rare/uncommon in Black Africans (publication 54). The rationale for this protection is that H. pylori gastritis affecting the corpus may produce a gastritis severe enough to cause a major reduction of gastric acid secretion and a substantial elevation of gastric pH when compared to subjects who are not H. pylori infected\(^4\). As a corollary the decreasing rate of H. pylori in developed countries will result in more effective preservation of acid secretion into old age, with a consequent greater prevalence of reflux esophagitis and its complications.

**Conclusion**

H. pylori infection is ubiquitous in Africa and acquired in childhood, yet complications associated with the bacterium are variable, unpredictable and particularly with regard to gastric cancer, generally low. Reasons for this inconsistency are unknown. A suggestion is that immune mechanisms play an inhibitory role. Paradoxically H. pylori infection may be protective against gastro-esophageal reflux and its complications. The hypothesis can be tested by further studies which investigate the correlation of H. pylori status with the
topographic extent and severity of gastritis to occurrence of reflux disease. Positive results will question the policy of global eradication of H.pylori (publication 54).

References

The PhD-thesis of Isidor Segal about his work in Soweto consists of the introduction (chapter 1) and 15 publications selected by Prof.dr. G.N.J. Tytgat and Dr. C.J.J. Mulder (chapter 2-16). Publication of the selected list of articles, as shown is his Database of digestive diseases in Soweto, would be too much for an PhD-thesis.

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