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# THE LOGIC OF DYSPEPTIC ULCER

By

M. L. KOTHARI AND JYOTI M. KOTHARI

## SUMMARY

*The cause and cure of a peptic ulcer are where medicine is least likely to look for—in medicine's irreverence for the vitally evolved acid, stomach and the pylorus, and in man's indifference towards their irrepressible urges, and needs. The so-called peptic ulcer is the dispensable tip of a dyspeptic iceberg, the dyspepsia, with or without duodenitis, giving rise to a symptom-complex that bears little correlation with what the physician can observe, investigate or measure. Medicine's unabashed ignorance of dyspepsia/duodenitis/ulcer allows one to fall back on the patient for setting himself right. The best thing about the dyspeptic complex is its readiness to disappear. Dyspepsia, duodenitis, ulcer therefore represent a state of ill-being, and not of pathology, visceral or psychic.*

A recent article[32] in the BMJ drove home the point that modern medicine's strongpoint is its unmitigated ignorance about all the major problems it contends to be researching upon and solving. Such holy ignorance allows medical men to do all that they fancy, for *a la* Albert Camus, *no one is wrong when no one is right.* Peptic ulcer has been one such problem, the illogic of which was presented earlier.[31] We now present incontrovertible *scientific* data to emphasize that what has been plaguing human stomachs and duodena is not peptic ulcer, but a symptom-complex that can only be labelled as dyspepsia,[10, 24, 39, 51] a culmination of which can be an ulcer. Also underscored is the fact that an appreciation of the marvels of human GI tract can empower medical men to rely more on their patient's gut-feelings and the resilience of their gut to set their dyspeptic problems right. Since the field to be covered is vast, it is imperative to present only the points on the various aspects.

## Phylogeny

1. Stomach, pylorus, pepsin, and HCL —targets of an ulcer-therapist—are the most consistent vertebrate features from fishes to ferrets, mouse to man.[16 46] Even the J-shape of the gastrum is a common feature "in forms as far apart phylogenetically as sharks and man."[46]

2. Stomach, through its pylorus is the guardian-angel of the *sanctum sanctorum* formed by the small intestine beyond, taking care to see that the latter *gets* just

*From: The Department of Anatomy, Seth G. S. Medical College, Parel, Bombay-400 012.*
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the right chyme, right in every conceivable way.[7, 12, 21, 28, 46]

3. The fact that the so-called peptic ulcer is only a man's privilege acquits the alleged culprits, on strength of the experimentalistic assumption that man and mouse are no different.

4. It is therefore likely that man's ulcer is a manifestation of his avoidable quarrel with his integral phylogeny, the quarrel springing from his being "civilized"[17] and thus hurried, harried, and a little too rational to be natural. JBS Haldane has remarked somewhere that a man is too careful about what he puts in his car, and not one-tenth as careful about what he puts into himself, and how.

5. Man with his exaggerated orificial pleasures is an animal that is ever ready to transgress the "Pray, do not eat/drink now" call from within. The socialization of the orificial instinct in man has robbed him of the life-giving/bliss-giving role of food. With the intrinsic rhythm and urges connived at, he has made dyspepsia into a virtue that supports an entire industry manufacturing digestants.

**Anatomy**

The enormous vascularity, innervation —"a unique vagal dowry"[13]—musculature and the presence of *the only definitive*[46] sphincter of the gut *viz.*, pylorus, bespeak Nature's rule that all these are there as they are needed. So is true of the chief and the parietal cell mass. Stomach, pylorus and duodenum behave as a unit[12, 28]—the gastroduodenal pump. "The exact mechanism of control of the transfer of stomach contents through the pylorus into the duodenum is still not fully clarified."[19]

**Physiology**

1. "O! it is excellent/To have a giant's strength, but it is tyrannous/To use it like a giant." *A la* Shakespeare, stomach does not use its powerful musculature for pushing things into the delicate duodenum. "By far the greater part of the work is utilized in mechanical digestion, serving to macerate the food particles and break them up into small fragments."[12] Stomach, as it were, gizzards the food (and wishes that man's teeth could ease its task).

2. Pyloric antrum, canal and sphincter are ultrasensitive mechanisms that know food from a fly, gruel from gravel, high pH from low pH, osmolar variations, chemical composition and so on. A primitive response is to shut down the sphincter whenever it is *felt* that the contents cannot be passed on into the small intestine. May be, it is this that prevents too rapid a loading of the circulation by fat.

3. Notwithstanding the above, patency of the pylorus[7, 12, 21, 50] is a rule, allowing whatever acid is produced in the stomach to be passed on into and quickly neutralized by the first part of duodenum.[7, 15, 19, 21] "Recent investigations of the disposal of acid by the human duodenum indicate that there is a marked capacity of the duodenal mucosa to dispose off acid by the combined mechanisms of neutralization, dilution, and insorption directly through the duodenal mucosa."[49]

4. Modern medicine knows everything about HCl secretion except why it is there —like the sentry in Quiller-Couch's *Zarina's Violet*. HCl secretion—the hunchback of Gastre Dame—obliges the body with a quick input, molecule for molecule, of bicarbonate into the blood which then is secreted by the pancreatico-biliary-intestinal system.[33] HCl secretion gives a net gain of alkali when (a) am-

photeric foods (protein) neutralize the gastric HCl, and (b) gastric HCl is thrown out by vomiting. HCl secretion is a good indicator of the state of acidosis/alkalosis: In the former,[27] as may be induced by HCl infusion, the rate of HCl secretion goes up; in the latter, as may be induced by $NaHCO_3$ infusion, the rate goes down.[33] The increased secretion of HCl in states of burns, stress, pulmonary insufficiency etc. is a reflection of the acidotic state to which the body is subject. In the GI turnover of acids and alkali, HCl secretion sets the pace.[33] The ravages[3] of ulcer surgery are partly because of the removal of this pacemaker.

4. The pyloric-duodenal interrelationship is such that acid in that area acts as an antacid by inhibiting gastric secretion of HCl.[4] (Here lies one cause of the failure of medicinal antacids). Even the rate of gastric emptying is controlled by the duodenal receptors, which are supposed to be working less effectively in duodenal ulcer cases, as compared to normal people.[48]

5. The GI tract is "the principal endocrine organ of the body"[43] there being more endocrine cells in the stomach, in number and types, than in the pituitary. The increasingly recognized gut hormones control everything that the gut does—peristalsis, sphincteric action, secretion, digestion, absorption, and more. Some of the hormones find way into the general circulation to possibly produce such symptoms as migraine and headache associated with GI-upsets and stress. Many a psychosomatic problem associated with a visceral (peptic) ulcer is a function of hormonemia. The hormones probably account for Palmer's observation that "All visceral lesions cause the same symptoms."[41] backed by the fact that "The trouble with the gastrointestinal tract is that it is so repetitious, both anatomically and physiologically."[41]

**Etiology**

1. In incriminating[26, 27, 40, 44] acid-pepsin for ulceration, medicine tells only half the truth (!). "A biopsy taken through the gastroscope heals as quickly when the acidity is high and continuous as in cases of hypochlorhydria."[5] Wide surgical incisions and mucosectomized gastric areas heal rapidly.[17] The other half of the truth, then, that medicine fails to tell is the realization that peptic ulcers have "a remarkable tendency to heal,"[35] in the teeth of the very acid-pepsin that allegedly caused them. May be, acid-pepsin helps healing of peptic ulcers.

2. Virchow raised the problem: If acid-pepsin are responsible, why not the 360° and the length and breadth of stomach and duodenum? Why should an ulcer be localized[5, 16, 38] to a single small, punched out area? Why is acute perforation of an ulcer not seen in more than 2 per cent of patients[26]? And why does the perforation-hole itself remain so small despite the alleged peptic onslaught? And having occurred, why does even a perforated ulcer heal,[26] *a la* Hermon Taylor, without a thing being done to the culprits? Dear Aunt Acid,[2] doesn't after all seem to be as unkind as portrayed ulcerologically.

3. Granting that acid-pepsin are etiologic, de-etiologizing the patient medically or surgically makes the matter worse. The illogic peptic dogma "no acid, no ulcer" perpetuates "yes acid, yes ulcer," a notion fed by such elegant ads—"In a few minutes his antacid will stop working. What Then?"[1] What use is an antacid, if it stops working in a few minutes?

**Normality of Distribution**

1. Like in all other fields of modern medicine, ulcerologists know (and treat) hyperchlorhydria/hypochlorhydria without knowing/defining the missing middle —euchlorhydria.

2. Average acid output is in no way normal acid output. "The range and not the average is the reality."[6]

3. HCl secretion is a biologic trait that is, like most other traits, *normally* distributed,[11] in its intensity. Cases of ulcer/hyperacidity fall equally on either side of the midpoint of the bell-shaped curve. "It is clear that among men and women with duodenal ulcer the lower levels of gastric secretion are equally common."[11]

4. The same individual has "hyperacidity" at 1.0 p.m. say, and no acidity 15 minutes after, on its own. What truly he has had, and may have again, is *acidity* —the consciousness of having acid within. Once and forever, the term hyperacidity[40] can be logically replaced by the level-non-committal *acidity*.

5. The normality of distribution extends to the age incidence of the onset of gastroduodenal ulceration, as well the age incidence of ulcers found at autopsy. "The peak of age incidence of gastroduodenal ulcer is the same as the period of arterio-sclerosis and other serious diseases of old age."[54] Just as the tails of the Gaussian curve stretch to infinity,[45] "new" cases of ulcer occur in the youngest to the oldest.[54] As far as HCl secretion and its alleged by-product ulcer go, we are dealing with a biologic phenomenon about which, like cancer or coronary, no one seems to know anything.

6. Point 5 above could drive home the point that not heredity but polygenic inheritance[45] mediates the so-called susceptibility to acidity and ulceration. The other side of the coin is that these are the people who need to be a bit extra careful about their gastroduodenal physiology.

**Pathology**

1. With all the symptoms, the so-called ulcer is so often absent.[10, 39, 51]

2. The much-prized ulcer has turned out to be the dispensable tip of the dyspeptic iceberg; it is a late event[10, 39, 51] in the history of an individual's dyspepsia, a final evidence that he and his physician have failed the patient's complexer-than-a-computer gastroduodenal region.

3. "The most important lesson has been that a great deal of organic gastrointestinal diseases—ulcers, tumours, gall stones, etc.—never cause symptoms or cause symptoms only very late in the course of things. The most seasoned clinician must continuously wonder how organic lesions of the same location, size and nature can produce symptoms of such differing intensities and apparent importance in different patients."[41] The Boydian[5] stock-title *The Relation of Symptoms of Lesions* is of little help in gastroduodenology.

4. The most natural tendency of an ulcer is to burn itself out. John Fry,[18] M.D., F.R.C.S., from a wide experience with peptic ulcer found in his *general practice*, gave a profile of the disease to conclude that, apart from the natural remissions uninfluenced by medical treatment, there was "a very definite likelihood, in both duodenal and gastric ulcers, for the condition ultimately to 'burn itself out' naturally and spontaneously." This natural burning out cures the ulcers in doctors without any operation,[31] but the medicos have no such patience[44] for their patients' ulcers. Such authoritarian-

ism was long enunciated by Mayo.[37] "Unfortunately, only a small number of patients with peptic ulcer are financially able to make a pet of an ulcer"—a teaching that is yet to burn itself out in surgical training.

**Clinical Features**

1. Ulcerology has not escaped medicine's text-bookish[26, 27, 35, 44] attempts at typicalizing what is, ulcer or no ulcer, so atypical[41, 51] at an individual level.

2. The atypicality arises from the ability of the disturbed gut—dyspepsia—to promote symptoms, visceral/psychic/somatic, ranging from heaviness to harriedness, distension to depression, vomiting to vanity, nausea to nervousness, and flatulence to flushes.

3. Dyspepsia is the most compelling feature; the overall symptomatology is varied, each symptom fleeting in character from hour to hour, with very little correlatable pathophysiology to account for the presence or the absence of a symptom or a sign.

4. Dyspepsia defies definition. In more general terms, it is the absence of instinctive friendliness with food and drinks—the welcome to food is reluctant, the after-food feeling is one of unease. There is an inability, *a la* Harris,[22] of the person and his GI tract to declare, "I'm OK, You're OK."

5. Much against Hurstian concept of diatheses,[40] ulcer/dyspepsia is every human's privilege: "As far as we know, the disease is available to all, at any moment. This means that it must be due to a physiologic deficiency or excess—some abnormal activity that is quickly available among the physiologic functions of everyone, to throw some built-in protective device out of balance."[41] More about it anon, but it could be suggested right here that the protection lies in pyloric patency that allows no damming back of acid. Should it occur, and should the stomach with its might force the acidic contents as a jet directed towards the duodenum, duodenitis/dyspepsia/ulcer could occur. Restoration of pyloric patency cuts down the onslaught permitting relief/healing to occur.

6. The symptomatogenesis at the gastropyloroduodenal level is more functional than structural. The finer individual nuances of muscle tension, hormonal release, acid/alkali secretion, receptor-function, etc., create a situation that can be hellish for the patient without the clinician realizing why. The one consistent thing that produces pain is the stretching of gut.[41] It is a part of the common, non-medical teaching to keep one's stomach filled much below its brim. The unease of an overfilled stomach could be ascribed (a) to the tightly shut pylorus on one hand, and (b) the stomach musculature kneading and chyming its contents, against high intraluminal tension, on the other. Hormonemia may also be responsible.

7. Increasing recognition is now being accorded to the fact that dypepsia[16, 24, 39 51] is far more common than duodenitis, which probably is commoner than and precedes the clinically dispensable manifestation of an ulcer. The most important wage of dyspepsia is not an ulcer, which occurs late in a dyspeptic's life, but the gnawing absence of *joie de vivre.*

8. "Dyspepsy and cheerfulnes do not go together."[25] A dyspeptic is incapable of meeting the world in bouyant spirits, declaring, *a la* Kalidas: *Look to this day, this wonderful day.* Dyspeptic gut, through a primitive mechanism that may be important for our survival

in the biologic past, grips the mind viciously through the vagal dowry, creating an odd affective mixture of irritation, depression, fear, listlessness, and above all, a sense of ill-being. While our intellect functions in the newest and the most highly developed part of the brain, our emotions continue to be dominated by a relatively crude and primitive cerebral system.[36] "This situation provides a clue to understand the difference between what we 'feel' and what we 'know'."[36] A dyspeptic, with or without an ulcer, *knows* he shouldn't be irritated, but he can't help his *feelings*. He is in a dyspeptic vice.

**Investigations**

1. With the irrelevance[11] of acid estimation, the right place for the nasogastric tube and the suction-pump is in the museum.

2. Histamine-stimulated MAO[30] is highly academic, but hardly useful.

3. The "time-honoured method" of radiologic investigations is blighted by as many as 30 per cent false-negatives and 37 per cent false-positives.[47] To wit, listen to a physician-patient: "The pain was ripping me apart while they were working on me in the X-ray department, but the pictures failed to show the crater. So I was dicharged cured."[20]

4. Endoscopy[39,51] can help only if it can detect a lesion, which may still be irrelevant.

5. Investigations on how effective the surgeon's knife has been in destroying[23,31] the patient's physiology helps neither the patient nor the physician, as far as the patient's well-being goes.

**Therapy**

1. The glorious failures of therapy are iterated here to stress that a patient must treat himself.

2. Drugs, *a la* Sir Colenso Ridgeon in Shaw's *The Doctor's Dilemma,* are a dyspeptizing delusion.[52] How could the consistently unpalatable—nauseating—antacids do any good to the gastroduodenum that is in no mood ever to welcome the insipid pulp of mentholated $Al(OH)_3$?

3. Unpalatability is a peremptory inner judgment on the inacceptability of a thing. So for any diet fad—Sippy's or Bippy's. The evanescent relief afforded by antacids springs from the temporary elevation of pH that eases the task of pyloroduodenal region, possible reduction of muscle spasm, and thus, of pain.

4. Gastric irradiation,[42] supercooling etc., deserve to be mentioned only to be condemned for the barbarity.

5. Surgery[14] cures, by complicating[3,23,26,31,44] the problem.

6. An ulcer often heals despite the patient and his physician.

7. "The warmth of clinical art rather than cold science is still required to manage the patient with a peptic ulcer."[18]

**Epistemology**

1. "But nature gives her observer cause only for admiration at the simplicity with which she works, and for astonishment at the proneness of the human wit to explain any phenomenon which appears remarkable by means of infinitely greater and more incomprehensible wonders."[8]

2. Simplicity of approach, even when compelled by logic and/or biorealism, is not a particular weakness of modern medicine, thriving as it does on the Bombay-to-Calcutta-via-Rome approach—a gimmickry that makes the medical men look very learned, the patient's problems

insolubly complex, and the remedial measures expensive and intricate.[9] As a starting point, a 6-worded aphorism can help ulcerology a great deal: *If ulcers could heal, ulcers can.*

3. As a historian of science once put it, "Isn't it amazing how many things there are that aren't so?" Quoting thus, Alan Watts[53] cajoles us further: "The world becomes intelligible through amazing reversals of common sense, and, as Whitehead saw, the notions most worth questioning are just those which are most taken for granted. Science, too, is the game of hide-and-seek, for the scientist most skilful in basic research has the peculiar flair for realizing that the best hiding places are those where no one would think of looking: they are usually right out in the open. How often an important discovery floors us with its simplicity, with the feeling of, "Well, why didn't I see that; it was right under my nose!"

4. The solution to the dyspeptic/ulcerous problem is truly under our nose—in the area it occurs/afflicts. Some of the needed ingredients of the solution comprise (a) teleologism that compels us to realize that HCl, pylorus, and vagal dowry are no mistakes of our maker, (b) corrected causalism that clears acid-pepsin of any guilt, (c) humility that what is not thought of/done upon doctors' GI tract will not be exercised[31] on the patients, and (d) the Hippocratic *invocation* of *Primum non nocere*—the treatment of ulcer should not exceed, in mental, physical, visceral and material cost, the problems it allegedly gives rise to.

5. The 9 times greater projection of the gastroduodenum on the human brain rather than the other way round should drive home the point that the CNS is not the cause[26, 27, 44] of dyspepsia/ulcer, but its helpable victim.

6. Medicine had better diagnosed the *pillars of unwisdom*[29] upon which its impressive edifice rests. A principal monumental superstition, *a la* Koestler,[29] is medicine's measurementism/parameterism—"that the only scientific method worth that name is quantitative measurement; and, consequently, that complex phenomena must be reduced to simple elements accessible to such treatment, without undue worry whether the specific characteristics of a complex phenomenon, for instance man, may be lost in the process." The solution to the problems under discussion does not lie in our measuring MAO or urinary enterogastrone, but in knowing the ease/disease of a patient. This would entail a greater reliance on what a patient feels, and not on what a gadget shows, and a greater respect for the "intangibles and unapproachables"[29] of a patient's symptomatology.

7. The philosophism inherent in such an approach is ulcer-realistically defended by Palmer:[41] "The time has come in ulcer therapy for more philosophy and less technology."

## HYPOTHESES

### Phylogenic

1. The gastric production of HCl as "the universal acidifying agent"[16] is a design in acid-base-regulation.[33]

2. In absence of food, the natural pyloric patency permits the acid secreted to be totally and immediately neutralized in the duodenum. For a while that the pylorus closes, the body gains in alkali because of the HCl secreted and retained in the stomach.

3. Nature's master-stroke, in fortifying body's alkali reserves through HCl

secretion, lies in making stomach the rendezvous for the powerful HCl and the ingested, usually-alkaline life, called food. The alkali-gain is so much as to spill over the rigorously-conserving kidney, seen as the post-prandial alkaline tide in the urine. Man has a penchant for working against this scheme by consuming fermented/denaturalized foods that are poor in their alkali content.

4. The man-made alkalies—the so-called antacids—are no substitutes for the alkaline foods for the simple reason that the highly sensible pyloroduodenal region has evolved in the company of amphoteric foods, and not through the courtesy of Aluminium Hydroxide gel.

5. Since acid-base-regulation affects every cell in the body, gastric HCl secretion is a target of all the systems of the body including the endocrines.[30]

**Physiologic**

1. The GI tract is a neuromusculohormonal ensemble whose spokesman is the gastroduodenal region whose message, I'm OK, is conveyed by a code called appetite—Life's lust for life.

2. Equally, this inner voice is as unreserved and irrepressible in declaring I'm NOT OK by coding for the lack of appetite, a feeling that is beyond words but always accompanied by a sense of ill-being.

3. The enormous vagal dowry, apart from performing the medically-despised release of gastrin to promote acid secretion, is there to mediate visceropsychic bliss, or the absence thereof. Such bliss is every vertebrate's right.

4. The stomach could be looked upon as the Import House of a city called an individual. The sensitive but obstinate pylorus is the arch-angel that takes care of not only the gut beyond, but such processes as fat/carbohydrate metabolism, as also, say, the distantly placed bone marrow. The uniformly cold response that stomach accords to most wonder-drugs is, may be, one way of pylorus and Nature telling medicine that, any day, the error of omission is preferable to that of commission.

5. Although the stomach can accommodate to a oral orgy by distending to the point of resting its greater curvature on the urinary bladder, it best functions in the optimally-stretched state. The optimality is individual-specific—a state that should not encroach on the consciousness. Overeating is now recognized as a definitive form of Selyean stress.

6. Fasting—an empty stomach—is the most physiologic way of resting the gut and curing dyspepsia/ulcer. "At the same time I decided to break another rule of orthodox medicine, the one that says that the stomach of an ulcer patient should never be empty. I had an appetite of a horse, so I decided to suppress it. In other words I was going to do the very opposite to what I had been doing until then."[20] This confession by a medical man[20] who cured himself of a bad ulcer could be paraphrased for public use: Always have the appetite of a horse, but never hog. Let that sense of ease and comfort that accompanies unsatiated appetite prevail.

**Eupeptic**

1. Teeth, time and temperateness are indispensable tools for being kind to one's stomach.

2. Despite hitherto denial by modern medicine, eupepsia is a physiologic state, held as the starting-point of all health, by non-allopathic medical sciences.

3. In matters of oral import, the best de is WIDD: When In Doubt, Don't.
4. Like the Pascalian heart, the sto-ch has its own secret reasons for likes d dislikes about food. When in diffi-ty, the wisdom of the stomach is supe-r to the rationalization by the intellect.
5. As socializing elements, food and/ drinks are eupeptic only to the degree t they do not overstrain the entero-tic (alimentostatic) mechanisms.

**rspeptic**

1. Man is not born dyspeptic; he trains nself to be so. Children rarely show off dyspeptic demeanor.
2. Dyspepsia is dis-ease, not disease; appearance is its cardinal quality.
3. Dyspepsia is a long-protracted, re-rrent warning that eventually paves y for gastroduodenitis which long-con-ued can end up in an ulcer.
4. The symptomatology of dyspepsia is nanifestation of a number of interact-; influences—muscle spasm, mucosal itation, hormonal overaction and so on. e symptomatology is incapable of ng analyzed by modern medicine.
5. Dyspepsia is an agent that makes ll out of an inherent heaven. Milton nd Lord Krishna in Gita) could be raphrased to state that not so much e mind, but it is one's gut that makes aven or hell.

**cer: Causative/Curative**

1. An ulcer is a medal honouring long, speptic service.
2. Yet, each ulcer, like Mr. Dolittle *My Faid Lady*[34], is *willing, wanting, iting* to heal.
3. It is neither acid-pepsin (for DU) r bile (for GU) that causes ulceration, t the way they are delivered.

4. The gastric-might, the pyloric-tight and the duodenal target account for DU. Whenever the situation is such as forces the stomach to push against pyloric resistance, acid-pepsin is delivered as a jet on to a point in the duodenum. It is possible that gastric distension alters the direction of pyloric canal so that the jet, instead of jumping into the duodenal lumen, hits on the duodenal wall.
5. The ability of fasting to restore eupepsia may be exploited towards ulcer-healing—a thing practised successfully in the past.[31]
6. The complications of an ulcer are mere consequences of the continuation of factors that produce an ulcer.

The Greek invocation—*Gnothi seauton —Know thyself* could be practically paraphrased as a *Gnothi gastroduodenum—Know (thy) stomach and duodenum.* The acceptance of ignorance is the beginning of one's knowledge. Medicine's such acceptance, *vis-a-vis* dyspepsia/ulcer can mean ushering in an era of the realization that some of these problems are so highly individualistic that they are best managed by the patient himself. The patient may fail, but the physician will always. Such a concept hits directly at physicianly omnipotence. It is time we had hit more widely.

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reverse of the Golden Rule—the Nedlog Rule.

"One highly significant fact that showed how the Physicians and Surgeons in Rochester really felt about the operations for duodenal ulcer was that in all my 25 years at the Mayo Clinic I can remember only one of the many members of the staff with an ulcer who was operated on, and he was driven to it late in life by a complication." This is a damaging judgment against ulcerologists by none else than Walter Alvarez.[2] The scanning of the hospital records, in Bombay or Barcelona, is unlikely to reveal anything otherwise. *Curative surgery for peptic ulcer* was invented by the physician but for the patient. Let us listen to a doctor-patient:[19] "Two colleagues who were surgeons, called in one day to pay a social visit. They told me that sooner or later I'd have to have my stomach removed and the sooner the better. The thought of a partial gastrectomy was anathema to me. I didn't see the sense sacrificing a perfectly good stomach because of a little ulcer that could hardly be seen . . . and when I read about the postgastrectomy syndrome in the BMJ my mind was made up." Doctors have the advantage they read BMJ; their patients don't.

The Nedlog Rule may be defined as the therapeutic authoritarianism that enables a clinician to readily do something on a patient that he would rarely, if not never, get done on himself. The reasons for this, *vis-a-vis* ulcerologists, are not hard to seek. A leading text *Clinical Gastroenterology*[22] remarks that operations for peptic ulcer entail considerable interference with the anatomy and the physiology of the upper alimentary tract, and it is not surprising that a proportion of subjects suffer from minor or major complications following surgery. "An unexpectedly high proportion of patients," Jones *et al*[22] added, "treated for alcoholism have previously had a partial gastrectomy; the same is probably true for patients with drug addiction." Which gastroenterologist or physician, knowing of the dumping syndrome, diarrhea, pernicious anemia, alcoholism, and drug addiction, would rush into where angels may fear to tread!

**Etiologism**

Modern medicine thrives[36] on causalism, an endless exercise in weird etiologism that hunts for *the cause* of cancer, coronary heart disease, diabetes, senescence and what the human body may have, with the evergreen hope of either nipping the cause in the bud (prevention) or of providing an appropriate *anti-cause*, (cure). "All philosophers, of every school, imagine that causation is one of the fundamental axioms of science, yet, oddly enough, in advanced science, such as gravitational astronomy, the word 'cause' never occurs. . . . The Law of Causality, I believe, like much that passes among philosophers, is a relic of a bygone age, surviving like the monarchy, only because it is erroneously supposed to do no harm." (Russell[33]) The robust survival of causalism in medicine is, *a la* Bertrand Russell,[33] an evidence of medicine not being an advanced science. Anyone doubting the foregoing could read Burnet's *Genes, Dreams and Reality,*[6] and Malleson's *Need Your Doctor Be So Useless*?[26] Modern medicine is not a science, but a vast empiricistic enterprise.

Factors floated as *causing* peptic ulcer are many, but we could mention seemingly the most likely one—STRESS. The facile assumption that peptic ulcer is a

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# THE ILLOGIC OF PEPTIC ULCER

By

M. L. KOTHARI AND JYOTI M. KOTHARI

## SUMMARY

*The unmitigated failure of peptic ulcer therapy has prompted this overview of the epistemologic and logical fallacies of the principles and practice of ulcerology. The illogic, rooted in the very term peptic ulcer, assumes a crescendo momentum, to the detriment of the patient. Like many other fields, ulcerology is causalistically oriented, culminating in cure-all drives against the assumed cause—the acid-pepsin complex. A plea is made, on grounds scientific, to view the situation from a different angle, holding the ulcer as dyspeptic, and as such irrelevant to the pathology, clinical features and treatment.*

"Reason guides medical practice," said an enthusiast. "No," declared a wag, "It's fashion that governs it." The truth of the latter is seen in its most devastating form in the treatment of what has been conveniently called *peptic ulcer*. Asher,[4] in *Talking Sense,* describes the "Seven Sins of Medicine." Ulcerologists perpetrate similar sins which may be listed, at the outset, as

1. The exercise of NEDLOG rule
2. Etiologism
3. Dysteleology
4. Technocracy of straight-line-solutions
5. Iatrogeny
6. Calling one's geese swans
7. Experimentalism.

The need to appreciate the *illogic of peptic ulcer* has been well-stated by Palmer.[28] "Obviously the path we have been following for many years has led to no final answers on the ulcer matter, nor does it offer any hope that it ever will. Progress can be initiated only by challenging current concepts, of course. My plea is simply that physicians dare to do some original thinking about ulcer." A subsequent publication "The Logic of Dyspeptic Ulcer"[23] provides a reasoned, documented apposite to the present article.

## The NEDLOG Rule

Erik Erikson, the psychiatrist-philosopher, lays down, in *Hippocrates Revisited,*[15] "the Golden Rule which advocates that one should do (or not do) to another what one wishes to be (or not to be) done by." In the management of peptic ulcer, physicians have practised the

*From The Department of Anatomy, Seth G. S. Medical College, Parel, Bombay 400 012.*
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stress-disease is probably as remote from the truth as the view that malaria is caused by vapours arising from the swamps.[12]

Yet another favourite etiology is the uxorial one: "The view that a peptic ulcer may be the hole in a man's stomach through which he crawls to escape from his wife has fairly wide acceptance." (Anderson).[3] Therefore, declared another physician, a patient treated for peptic ulcer must change his life as well as his wife.[30] Life, wife, stress, acid, pepsin—not one of these can satisfy the fundamental tenet of *causalism*[16] that necessitates an invariant relation of events in which the *effect must follow the cause, every time.* The italicized tenet is betrayed by the ulcer, which, by its very nature, is waiting, wanting and willing to heal and often does so in the teeth of the very cause that caused the ulcer. It is like in cancer: Whatever that is claimed as *causative,* can be claimed with undiminished vehemence as *curative.*

**Dysteleology**

Dysteleology is the assumed absence of purpose in Nature.[35] It allows hubristic medicine to put Nature in the dock, to assume her guilt, and to declare HCl, breast or prostate as "A design nightmare for which Nature should hang her head."[31] Were it given to scientists, they would have long ago chopped off the hanging head of mother Nature!

*Vis-a-vis* peptic ulcer, dysteleology is the prevalent gastroenterologic doctrine, that medicine's failure to understand the *raison d'etre* of stomach, pylorus, vagi, and hydrochloric acid secretion is sufficient license to forever destroy one or all of these, in a given patient. Such an approach can be effectively cloaked by euphemisms like "curative surgery" or as "pyloroplasty." The very term pyloroplasty presupposes pyloric error; the procedure achieves no plasty but pylorolysis; the net gain to the patient is the loss of a physiologic marvel called the pylorus. "Although there is a temptation to regard pyloroplasty as a non-destructive operation there is accumulating evidence to the contrary."[11] The same authors[11] describe pyloroplasty as ulcerogenic, by its giving rise to an "incontinent stomach." The authors[11] added that these effects were to "virtually the same extent after both pyloroplasty alone and complete vagotomy and pyloroplasty."

**Straight-Line-Solutions (SLS)**

Modern ulcerology is a highly advanced diagnostic and therapeutic technocracy evolved out of what Gene Marine calls *The Engineering Mentality*:[27] "It comes about because, somehow, (we) have become fascinated with technique as the answer to everything. Our dawn and twilight devotions are in homage to 'know-how', and the straight-line-solution is our way of dealing with the questions of life, from seduction to South Vietnam." The SLS-oriented technocrat spots a "problem" and sets about remedying it, come what may. If the blood pressure is up, keep it down; if it is down, push it up. Until recently, for example, patients of hypovolemic shock were given vasopressors, and their blood pressure readings rose strikingly, to the satisfaction of all concerned, "except of the patients, who died."[38] If the portal venous pressure is up, go down and create an Eck fistula. What about the severe liver anoxia and the ammoniacal intoxication of the brain? Let the liver and the live-r manage.

In ulcerology, the villain-of-the-piece is gastric HCl and no technocratic

SLS has been spared—from the relatively benign antacids to the drastic measures of charring the stomach by irradiation, freezing it by supercooled alcohol, chopping it, *a la* Visick, to the point of leaving just a little fundic cuff hanging from the esophagus, and sacrificing the vagi. It was found that when vagi go, the pylorus ought to, hence pylorolysis called pyloroplasty. And to imagine that all the foregoing has been actively practised despite a "not-guilty" judgment in favour of HCl, announced way back in 1959: "Anyone seeking in a court of law to prove 'acid aggression' responsible for peptic ulceration would be dismissed after two-minutes' cross-examination with a stern admonition not to waste the court's time."[31]

The story goes a little further. The alleged culprit has been discharged with honour.[28] HCl has been shown to help ulcer patients. Newly-hospitalized patients with active duodenal ulcer were given 2 bedside bottles—one of $Al(OH)_3$ gel and the other of dilute HCl. The two 'drugs' were presented to each patient as alternative products for treating ulcer. The patient was asked to try one, and then the other in two ounces doses from time to time, and then to use whichever for him worked better. No other drug nor any special diet was given. All patients made fine progress, but their preferences differed. Of 230 patients so doubly-treated, 31 could see neither as useful, 106 felt better with $Al(OH)_3$ and as many as 93 preferred HCl. Palmer[28] remarked that both the antacid and the acid were little more than placebos—2 ounces of dilute HCl is not much acid, nor 2 ounces of medicinal $Al(OH)_3$ is much of an antacid. The whole trial drove home the point that ulcer patients can be treated "successfully" either with acid or antacid, neither having *anything* to do with the efficacy of treatment.

**Iatrogeny**

Allopathy, etymologically, is the art of curing one disease, by causing another.[35] Ulcer therapy represents an acme of scientific allopathy, having in its repertoire measures ranging from dietary invalidism or diarrhea to the dumping syndrome, and anemia to alcoholism. Palmer[28] observes that "classical therapy creates dietary invalidism, an illness that may be worse than ulcer disease." The insipidity of antacids, the gastric revulsion of forced milk feeding, the visceral atonia of vagolytics, the distension and diarrhea of vagotomy, and so on, are things that can be best described only by doctors who had had the privilege of being so treated, a privilege, alas, granted only to a few who seemingly haven't lifted their pen in protest.

The therapeutic efficacy of iatrogeny, much like the counterirritant effect of a pain balm that works by shifting the attention of a patient from one disease to another, when well worked-out may provide iatrogeny a respectable place in the therapeutic armamentarium of a physician treating, say, ulcer, cancer, or schizophrenia. A patient thrown from the fire into the frying pan is most likely to forget the fire because of the overwhelming presence and effect of the frying pan. The foregoing principle of iatrogeny-as-therapy can be ably assisted by the *placebo* effect not just of the drugs, but of surgery as well.

"Surgery as Placebo," a 1961 article by Beecher[5] cites considerable evidence to drive home the point, the placebo effect being the greater the more dramatic the surgery. The supreme indication of ulcer surgery is the failure of medical therapy,

a conceptual sequence that foresuggests the patient that when drugs fail, surgery steps in to succeed. Since *placebo*[10 35] (L. "I will please") has a strong pharmacologic ring about it, surgeons as a class find it extremely difficult to realise the placebo effect of surgery, unless they listen to Day[9]: "Apart from poisoning by stealth, there is no form of therapy from which the effects of suggestion can be entirely eliminated." As a pertinent example, Beecher[5] cites ligation of internal mammary artery to improve coronary flow—an operation that worked only through its placebo effect.

**Calling One's Geese Swans**

Asher[4] alludes to Crawshay-William's *The Comforts of Unreason*—unreason breeding "comfortable concepts." An important comfortable concept, Asher points out, is the therapeutic assumption that since what is given is treatment, it must be effective. The next step, *a la* Lewison[25] is to assume that one's therapeutic geese are truly swans, smarter than the geese in any other farm. Hence the innumerable drug regimens and curative operations, all being equal, but some being, depending on the therapist, more equal.

A properly controlled prospective therapeutic trial on the leading elective surgical procedures for duodenal ulcer exposed the myth of any goose being more swanish than another.[14, 18] An editorial annotation[14] declared that the findings "cast doubt on sweeping statements made by advocates of their own particular favourite procedure in the surgery of duodenal ulceration." Whatever the marginal advantages, they were more than offset by the fact that "the results of all operations tended to deteriorate gradually with the passage of time."[18]

A word about the "bewildering plethora of antacids available," which relieve ulcer pain but which affect neither the healing of an ulcer nor its recurrence.[28, 37] To be effective, any popular antacid must be given in a very large quantity, and at hourly, if not shorter intervals.[21 28 37] Thompson[37] makes 2 important observations: (a) "The ideal antacid is still not available," and (b) "no antacid is completely without side effects." Palmer[28] may sound harsh when he concludes that giving a patient "diet and antacids" is just a gesture—spurious and dishonest, working, when it does, only by its placebo effects.

Yet antacids alone cost the USA over 100 million dollars a year.[37] What held true in Alvarez's time at Mayo Clinic,[2] holds true today. Day in and day out, stomachs are chopped and vagi are cut —of the patient. Why this must-treatism? Asher[4] gives the answer. "It is better to believe in therapeutic nonsense, than openly to admit therapeutic bankruptcy." So the wheels of medicine keep on moving, be it cardiology or cancerology.[24]

**Experimentalism**

In a reputedly scientific book *Search for New Drugs*,[32] wherein the quest is for agents effective against all leading problems faced by modern medicine, a recurring refrain is *the absence of ideal animal experimental model.* Ulcerology is no exception. Yet, the book is at pains to describe the available major and practical techniques for "the rapid and effective screening of potential therapeutic agents."[37] In the laboratory too, it is much better to believe in experimental nonsense, than to admit experimental bankruptcy. It is little wonder, then, that anticancer drugs are 100 per cent effective in the laboratory and are 100 per cent ineffective by the bedside.[17]

Peptic ulcer, as medicine has understood it, is strictly a human privilege; what experimental models oblige with are simple gastric erosions that have not an iota of similarity with the human condition in terms of number, location, pathologic features, and natural history. Yet since the experimental ulcers serve research labs, drug industry and the FDA, they must be created by ingenious techniques that reek with intellectual compromise. The means employed, "to name a few"[37] are ligation of pylorus (Shay ulcer), stress, ulcerogenic (erosionogenic!) drugs, Mann-Williamson procedure, induction of chronic ribloflavin deficiency, stimulation or destruction of localized areas in the brain, and portacaval shunting.

**Peptic or Dyspeptic?**

The dictionaries[10, 35] are against the semantic misappropriation peptic ulcer: Peptic (Gr. *Peptikos*) means digestive or related to digestion. Peptic ulcer becomes *digestive ulcer,* a connotation that can make no sense. Even the clinical clinging to the word ulcer is wrong.[28, 34] The cardinal clinical reality and presentation is not ulcer, but *dyspepsia,* a term that encompasses the absence of commonly-experienced-but-yet-to-be-described epigastric bliss/euphoria on one side, and the presence of epigastric discomfort, fullness, pain, burning on the other. Dyspepsia is symptomatic dysgastria-dyspylorosia-dysduodenia. Ulcer is a dispensable symbol for this larger dyspeptic reality. It need not be there. If present, its right appellation is dyspeptic—dyspeptic ulcer. "Essential for understanding gastroduodenal ulcer as a clinical disease is the concept that the crater is simply a manifestation and is rather unimportant to the whole illness. Unfortunately the crater is the only manifestation that can be detected and measured by a laboratory test, and so the disease was named for it. One may reasonably insist that the presence of a crater is not necessary for the diagnosis of ulcer disease. If the underlying whole-body disease is present, it makes little difference to the diagnosis whether or not the manifestation is also present. It is not the ulcer that is causing the illness but the illness that is causing the ulcer." (Palmer[28]). Spiro[34] views it a little differently, preferring to call the syndrome eponymously as Moynihan's disease. Dyspepsia, duodenitis, and duodenal ulcer, he points out, are parts of the same spectrum. Over 80 per cent of dyseptic patients having no X-ray findings, eventually develop radiologically demonstrable crater within 6 to 27 years. Isn't it in fitness of things that peptic ulcer be called dyspeptic ulcer? The very etiologic word *peptic* misleads the therapist into wrecking the peptic mechanism comprising acid and pepsin. The appellation dyspeptic would surely serve as a deterrent against a surgical blade ready to chop the stomach or cut the vagi.

**Hyperacidity**

Albutt[1] lamented that "Our path is cumbered with guesses, presumptions and conjectures." He wrote these words about hypertension, but which are equally applicable to gastric hypersecretion and hyperacidity. In the very first page of his masterly monograph *High Blood Pressure,*[29] Pickering makes it clear that the term hypertension is wrong because no one knows the dividing line between *eu-* and hypertension. Nosophilic medicine has bred much of the *hypo-this* and *hyper-that* by disregarding the Ardreyan advice that *the range, and not the average, is the reality.* Barring such tumorous

situations as Zollinger-Ellison syndrome, HCl output exhibits a range, each point on the graph being normal for the owner. Cleave[8] rightly points out that "the law of adaptation indicates that the production of hydrochloric acid must be just as perfectly attuned to the requirements of the individual as is, for example, the power in his arms or his legs or any other part of his anatomy. Far from constituting a liability, the production of large amounts of acid in the stomach, passing under the term 'hyperchlorhydria', should be regarded as a most necessary asset." Pylorus, normally patent, allows the acid secreted to be passed on into the duodenum where it is immediately neutralised. Any situation—and these are many for the sensitive mechanism that is pylorus—that prompts the pylorus to close down creates automatically a damming-up of acid with resultant feeling of "hyperacidity."

What really, then, gives rise to hyperacidity is not hypersecretion but, if you insist on the prefix hyper-, hypercollection. The same can set up a vicious cycle, for acid accumulation forces pylorus to close tighter, designed as it is to protect the duodenum and small intestine from being damaged by too strong an acid input.[20] The pyloric wisdom of shutting down ought to be respected, and no further food load be added, lest its task becomes more complicated. It is little taught physiologic truism that the pylorus is a reliable and sufficiently vociferous spokesman of the state of the gut beyond: "In general, it probably can be stated that most of the control of the pylorus is exercised by the small intestine. As long as the duodenum and remainder of the small intestine are empty and are in a receptive state for chyme, apparently the pylorus relaxes, and the stomach contents empty easily, but irritation, excess fats, overloading, etc., can all make the small intestine less receptive for chyme and cause increased contraction of the pylorus. Therefore, even though the discrete details of the control of the pyloric sphincter are not known, the philosophy of this control appears quite evident."[20] Fasting as a satisfactory and successful treatment of peptic ulcer and hyperacidity was extensively practised for 50 years after its introduction in 1875.[8] The clinical experience of a husband reporting his revulsion at "regular milk therapy" forced upon him by his wife at the instance of the clinician is not uncommon. The doctor-patient referred to earlier[19] put it well: "With this careful and faultless treatment I became progressively worse. . . . I got worse and worse and fatter and fatter." Ultimately the cure for him came with the decision to "break another rule of orthodox medicine that the stomach of an ulcer patient should never be empty."

**Vagi, Dyspepsia, Eupepsia**

Finally, a word about vagotomy, which is but a glorified form of sensory neurectomy. The vagus is 90 per cent afferent, just 10 per cent efferent.[7] This makes the gastroduodenal projection on the CNS at least 9 times greater than the other way round, making peptic ulcer/hyperacidity symptomatology a manifestation of visceropsychic disease rather than otherwise. It accounts for the overpowering mental symptoms accompanying dyspepsia—irritability, depression, headache, lack of concentration and confidence, and what not.

The enormous gastroduodenal projection on the CNS works two ways—on one hand it produces *dyspepsia,* but equally on the other hand, it mediates eupepsia—

peptic bliss which ulcerologists have not described, violating thus the Asherian[4] advice that one can't describe the abnormal without first describing the normal. Dictionaries[10 35] go at length in describing dyspepsia; eupepsia is not given a place,[35] or is described as "the presence of normal amount of pepsin in the gastric juice."[10] Eating food illustrates the biologic principle of life assimilating life. Eupepsia is the visceropsychic readines to welcome the guest-life, and having ingested the guest-life, to feel really nice till the guest turns host through digestion and absorption. Should it be any more surprising that individuals surgically deprived of this ability to enjoy eupepsia turn to alcohol and drugs[22] to find some *raison d'etre* of their existence?

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# SALT FREE DIET FOR PEPTIC ULCER

M. L. Kothari, A. B. Vaidya, J. C. Doshi and U. K. Sheth

One of us, (M.L.K.), when on salt-free diet, for reasons altogether different, expressed complete relief from the symptoms of gastric hyperacidity of long duration. This observation prompted us to study the role of salt-free diet on the gastric secretion of hydrochloric acid (HCl) in patients with peptic ulcer and/or hyperacidity. Salt-free diet means total avoidance of common salt (NaCl) in cooking and eating. Certain observations about the relationship of the chloride ion and the gastrointestinal tract have been published.[4]

## MATERIAL AND METHODS

Seven male subjects, average age thirty-three years, were studied. Six cases had duodenal ulcer and one had hyperacidity. The average duration of symptoms was eight years. All the ulcer cases were considered intractable and had been advised operation.

While on usual (salted) diet, the patients were assessed clinically and the gastric secretory response studied by the method of Kay.[3] The patients were then put on salt-free diet. After an average period of fourteen weeks on salt-free diet, a repeat study of gastric secretion by Kay's method was made. The patient (M.L.K. No. 1, Table No. I), with only hyperacidity, underwent six secretory response studies, both on salted and salt-free diet — a total of twelve gastric analyses.

The procedure employed for studying the secretory response by Kay's method was essentially the same as described by Baron,[1] with observation of all the necessary precautions. However, the basal secretion was collected for only 30 minutes and each specimen was titrated to neutrality (pH = 8) against N/10 NaOH, using phenolpthalein as the indicator. The results (Table No. I) are expressed as the maximum acid output (M.A.O.) as defined by Marks and Shay[7] i.e. HCl output in mEq./hour.

TABLE I—*Maximum Acid Output*

| | A | B | |
|---|---|---|---|
| Patient | Salted regime (mEq./hr.) | Salt-free regime (mEq./hr.) | Percentage fall in A |
| 1 | 43.88* | 27.73* | 36.40 |
| 2 | 17.44 | 15.47 | 11.30 |
| 3 | 29.84 | 24.64 | 17.43 |
| 4 | 36.98 | 33.49 | 9.44 |
| 5 | 41.80 | 18.72 | 55.21 |
| 6 | 53.02 | 21.26 | 59.88 |
| 7 | 28.45 | 22.84 | 21.87 |
| Av. | 35.91 | 23.45 | 30.22 |

* Average of six consecutive analyses $P < 0.01$.

## RESULTS

### Clinical

The onset of relief from symptoms was noticed after being on salt-free diet for about six weeks. Complete relief was obtained after an average period of nine

From Departments of Anatomy and Clinical Pharmacology, Seth G. S. Medical College, Bombay 12, India.

weeks. By this time, the epigastric tenderness had disappeared. The therapeutic benefit was found to be well-sustained over a minimum follow up of nine months to maximum of thirty-six months.

### Gastric Secretory Response

The M.A.O. on salt-free diet was significantly lower than that on salted diet (P 0.01) as shown in Table No. I.

## DISCUSSION

Lahiri[6] has shown fall in HCl output on diet free from common salt. Undoubtedly, the ultimate source of gastric HCl is the sodium chloride in blood.[8] Kahn,[2] long ago, succeeded in producing acid free gastric juice by prolonged feeding of animals with chloride-free meat. The withdrawal of common salt has multiple effects, all of which tend to diminish the secretion of acid by parietal cells.[5] The authors feel that the stomach excretes HCl, rather than secretes it[4] and this physiological function of the stomach can be suitably altered in cases of peptic ulcer and hyperacidity.

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# *RAISON DETRE* OF HYDROCHLORIC ACID SECRETION BY STOMACH

**M L. Kothari,* A B. Vaidya,** J C. Doshi,** U K. Sheth****

"A fact in itself is nothing. It is valuable only for the idea attached to it, or for the proof which it furnishes."—**Claude Bernard**

The cause of continuous gastric secretion of hydrochloric acid (HCl), in absence of food is one of the great unsolved problems of medicine[35]. Physiologists have been unable to assign any convincing function to gastric HCl secretion which is incessant, enigmatic and apparently needless.

Certain bold assumptions, supported by clinical and experimental observations have permitted the formation of a concept of the functions of gastric HCl-secretion.

**Accepted Functions of Gastric HCl Secretion[20,40].**

The functions assigned, at present, to HCl secretion are that it—(i) assists in peptic digestion, (ii) helps in iron absorption; and (iii) serves as gastro-intestinal antiseptic agent.

That these functions are relatively insignificant is borne out by the following facts. HCl is secreted continuously and the intragastric acidity is often high during fasting states[1,8,17,35]. Patients with duodenal ulcer secrete from 3-20 times as much HCl in the fasting state and at night as do the normal persons[8,17]. Gastric (peptic) digestion can go on over a much wider pH range than has normally been accepted[23]. Absence of HCl secrtion causes no digestive abnormality[1,20,35]. Stomach is unimportant for digestion and absorption[1]. These findings rob HCl secretion of any significant role in peptic digestion. The role of HCl in iron absorption is questionable[19,38]. Normal iron absorption can occur in achlorhydric individuals[1,19,20,40]. Isotope studies in man and animals show the alimentary absorption of iron-salts to be the same in the post-gastrectomy subjects as in the normal subjects[3,10,37]. The antiseptic effect of HCl is more of an *idée fixe* since achlorhydric and hypochlorhydric humans are none the worse for its absence[1,35], nor are those with it in normal or excess amount any better off. Bacterial count up to 1,00,000 organisms per ml. of normal gastric juice may be found[40]. The complacency of a surgeon after a gastrectomy (of the patient!) arises from an unwritten conviction that the stomach and its HCl secretion have hardly any function. Gastrectomy is anatomically mutilating and physiologically disturbing[38], nay sometimes devastating, provided the functions of the stomach and its HCl secretion are viewed in a proper perspective.

**Physiologic Changes on Gastric HCl Secretion:**

1. Addition of an equivalent quantity of alkali to the blood:

For every molecule of HCl secreted, the stomach sends a molecule of $NaHCO_3$ into the circulating blood[13,14,35,40], a part of the extra-cellular fluid compartment or the *milieu interieur*.

2. Alkaline tide in the blood and urine:

From the Departments of Anatomy* and Pharmacology**, Seth G. S. Medical College Parel, Bombay-12, India.
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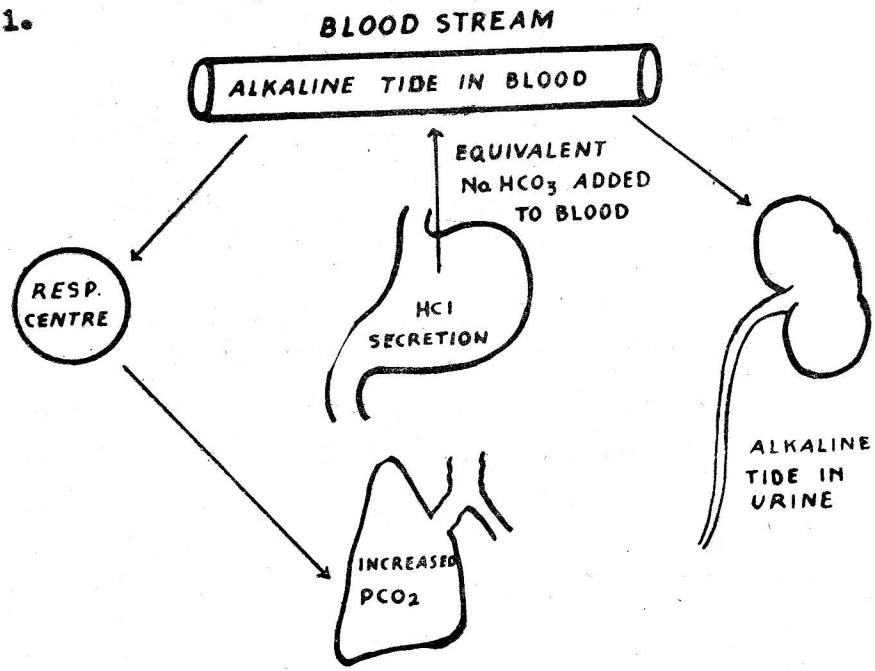



*Fig. 1.*—Shows the various physiologic changes on gastric HCl secretion.

The flow of large quantities of $NaHCO_3$ into the blood produces "positive alkali balance" and this is responsible for the post-prandial alkaline tide in the urine[14,35,36,40]. When HCl secretion is reduced or absent, the alkaline tide in the urine is diminished or fails to occur[36].

3. Rise in $pCO_2$:

The rate of $C0_2$ elimination by the lungs diminishes, leading to a temporary rise in $pCO_2$[40].

Changes 2 and 3 indicate the correlation[26] in the functioning of the stomach, the lungs and the kidneys (*vide infra*).

**Suggested Functions of Gastric HCl Secretion:**

I. Elimination of a strong acid from the blood.

II. Enriching alkali reserve of the blood (and hence of the body).

III. Partaking in the acid-base chain in the digestive tract, vital for the pancreatic, intestinal and biliary (P.I.B.) secretions.

IV. HCl reaching with the $NaHCO_3$ of P.I.B. secretions, gives rise to an endothermic reaction with evolution of $CO_2$ which has a salutory effect on the action of enzymes.

I. Elimination of a strong acid from the blood.

By secreting HCl into its lumen, the stomach eliminates a very strong, mineral acid from the blood (*milieu interieur*) to the outside (*milieu exterieur*) (Fig. 2).) Stomach is essentially an organ of acid-elimination and alkali-production and its primary allegiance is to the system of acid-base regulation in body[26]

Stomach secretes (or excretes)[24] HCl in 98 men out of 100[40]. It elaborates this secretion in which the $H^+$ ions are about 4,000,000[14,20] times more concentrated than in the blood at $pH < 1$[9].

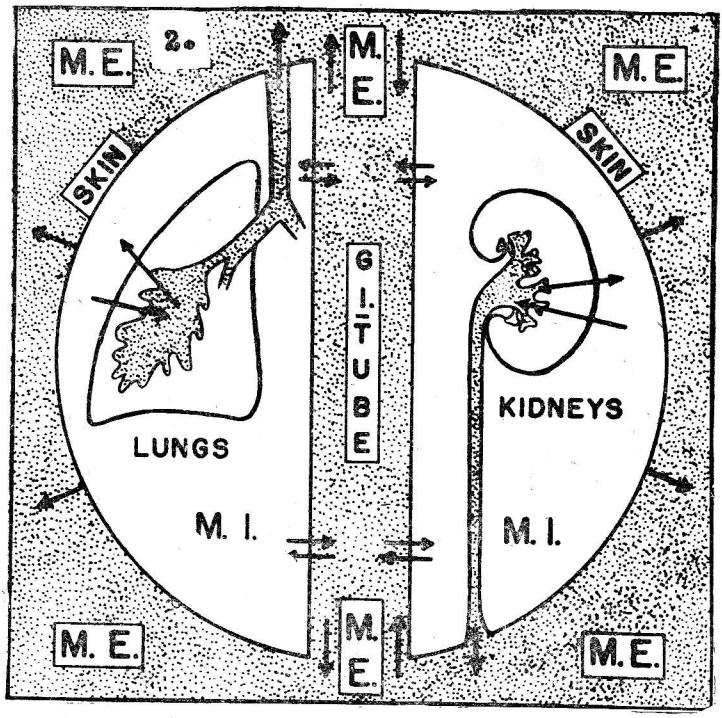



*Fig. 2.*—shows how the lumen of the digestive tract forms a part of the *milieu exterieur* (ME). The digestive tract lining separates the ME from the *milieu interieur*. (MI)

The maximum acid output by the stomach in man can be as much as the equivalent of 500 ml. of 0.16 N HCl in one hour[9]. This works upto 80 mEq. of HCl per hour (cf. kidneys). Wright[40] mentions the standard acid output, per hour, under maximum (histamine) stimulation, as 182 ml. of 0.1 N HCl which comes to 18.2 mEq of HCl per hour. The kidneys can throw out acid at the rate of 4-6 mEq. per hour at maximal rates of excretion[33].

At this juncture, a comparison may be usefully drawn between the stomach and the lungs, and the stomach and the kidneys, the trio being important in acid-base regulation[26].

1. Both are (a) developed from the foregut[22], (b) richly vascular with presence of a-v shunts, and profuse blood flow[4,9,18], (c) innervated by vagii[35,40].

2. Both are concerned with continuous elimination of acid from the body to the exterior.

3. When stomach eliminates more HCl, the lungs compensate by eliminating $H_2CO_3$ at a diminished rate[40], and *vice versa*[7].

4. When the lungs fail in eliminating $H_2CO_3$ adequately (hypoventilatory lung diseases), the stomach compensates by eliminating greater quantities of HCl, resulting in the well-known hyperchlorhydria and peptic ulcer, secondary to lung diseases[34].

Continuous HCl secretion by the stomach, even in absence of any food, should be considered as natural and physiologic as the continuous elimination of carbonic acid by the lungs. Putting it crudely in mathematical terms, it may be stated that—

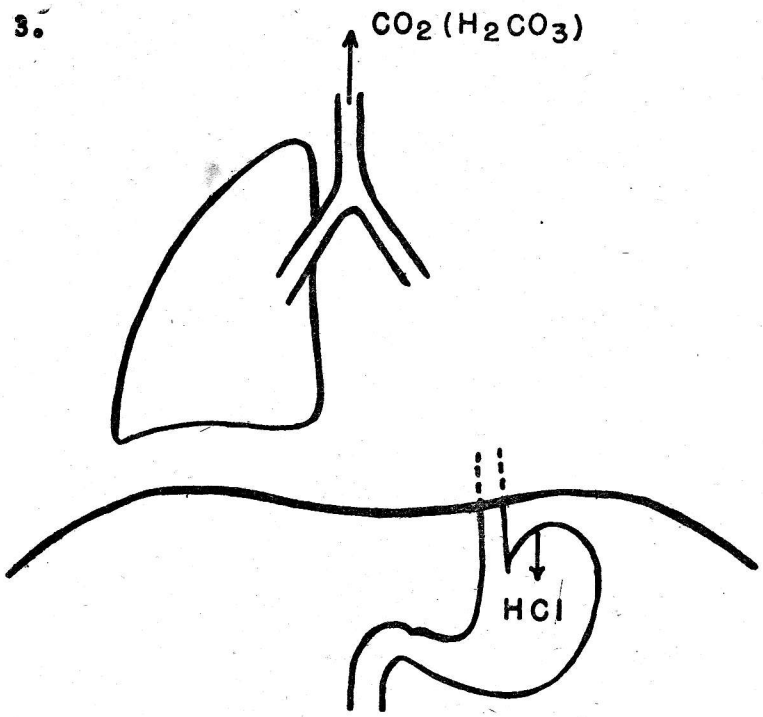



*Fig. 3.*—shows the two derivatives of the foregut, supra and subdiaphragmatic. engaged in constant elimination of acids from the body to the exterior.

$QH_2CO_3$+QHCl=K where, $QH_2CO_3$=Quantity of the acid eliminated by the lungs per minute (say), QHCl=Quantity of the acid eliminated by the stomach per minute and K=the constant quantity of acid ($H^+$ ion) that should be eliminated jointly by the stomach and the lungs per minute for the pH-constancy of the blood (*milieu interieur*).

**Stomach and Kidneys (Fig. 4):**

With no apparent similarity, the stomach and the kidneys are similar from more than one angle.

| | Stomach | Kidneys |
|---|---|---|
| 1. | Eliminates fixed acid HCl[35,40]. | Eliminate HCl and other fixed acids[33]. |
| 2. | Adds quantitatively to the blood-base[13,14,20,35]. | Of the base returned to the blood, 3/4th is passively re-absorbed while only 1/4th is actively added by excretion of $H^+$ ions[33] |
| 3. | Gastric tubules directly secrete H† ions[13,14]. | Renal tubules directly secrete $H^+$ ions[32]. |
| 4. | H* ion gradient Stomach: Blood: 4,000,000 : 1[14,20] | $H^+$ ion gradient Kidney : Blood :: 800 : 1[33]. |
| 5. | pH gradient Stomach : Blood ::1 : 8[20,35]. | pH gradient Kidney : Blood :: 4.5 : 8.2[33]. |
| 6. | Rich in carbonic-anhydrase and dependent on the same[1,14,35]. | Rich in carbonic-anhydrase and dependent on the same[33]. |

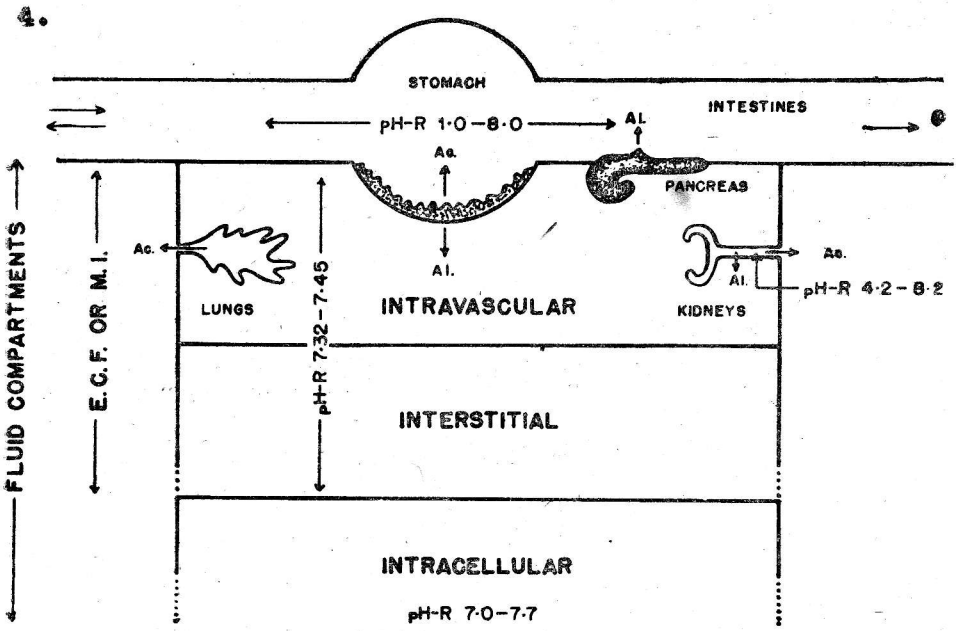



*Fig. 4.*—A comprehensive scheme to show the various fluid compartments of the body and their pH-range (pH-R) in health. The avenues of communication between the *milieu interieur* (MI) and *m. exterieur* are shown. Ac=Acid; Al=Alkali.

| | | |
|---|---|---|
| 7. | Very vascular with profuse blood flow[4,9]. | Very vascular with profuse blood flow[33]. |
| 8. | Presence of a-v shunts[4]. | Presence of a-v shunts[27,34]. |

9. Both are interconnected in the acid-base regulation of the body[26].

10. Both form a part of the "Chloride Excreting Cell Mass" of the body[25]

11. Mar *et al*[29], resorted to gastro-dialysis in acute kidney failure and obtained chloride removal at rates of 139-275 mEq./24 hours with mean of 224 mEq./24 hours.

During high rates of acid secretion, the stomach is removing both $O_2$ and $CO_2$ from the blood, and has a negative respiratory quotient[14]. Thus, the stomach not only eliminates $H^*$ ions from the blood, but also $Cl^-$ ions and $CO_2$, both of which are acidogenic[36]. The stomach responds to acidosis and alkalosis in ways befitting an organ of acid-base regulation, tending to restore the pH-constancy of blood by altering its secretion of HCl. Stomach is a highly sensitive pH-stat. As an immediate corollary of the above statements, it may be stated that the vagaries of HCl secretion are an expression of the acid-load thrown onto the stomach, under conditions of health and disease[26].

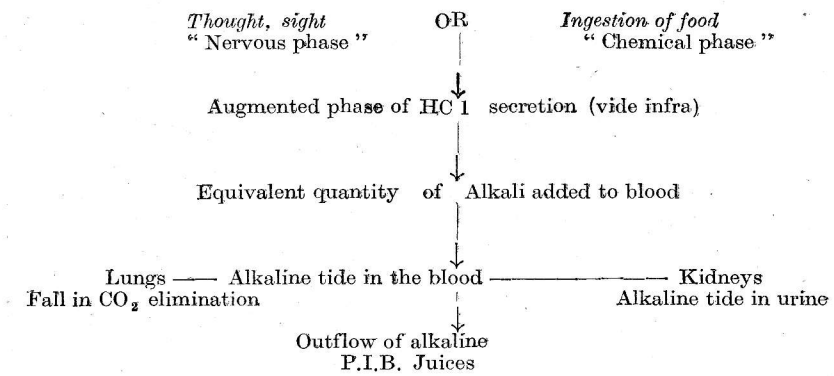
II. Enriching alkali reserve of the blood:

From the foregoing, it is clear that the stomach is more important than the kidneys, in the fortification of the alkali reserve of the blood, and hence of the body. It eliminates a strong acid on one side and *pari passu* actively adds alkali on the other, a role played neither by the lungs nor the kidneys (*vide supra*). For long, stomach has been blamed for secreting large volumes of HCl. Justice would be done to the stomach by saying that its more important function is the fortification of the body base.

III. Partaking in the acid-base chain in the digestive tract: By its secretion of HCl, the stomach partakes in an important acid-base chain in the digestive tract, thereby paving way for the pancreatic, intestinal and biliary (P.I.B.) secretions. The *modus operandi* in achlorhydria has been discussed elsewhere[26].

It has been mentioned that the alkaline P.I.B. secretions flow to neutralise the acid secreted by the stomach[35,40]. We suggest, here, an unconventional chain : HCl is secreted, as first thing during digestion, so as to produce the vital, "positive alkali balance" in the blood, thus permitting the outflow of large volumes of alkaline P.I.B. scretions from the blood into the intestinal lumen (Table 1).

TABLE 1 :—*The Acid-Base Chain During Digestion* :




The word oxygen means generator of acid[40]. Body metabolism, utilising oxygen every moment, incessantly produces acid substances. The crying need of the body, every moment, is elimination of acid and conservation of base. The importance of the latter will be realised from the fact that the resorptive power of the kidneys, for bicarbonate (base), is 99.95% efficient under ordinary conditions[30] This data would suggest that the blood cannot lose a large quantity of alkali (base) to the exterior unless its alkali-reserve is fortified in advance.

Table 2 shows that a very large quantity of alkali is poured out, periodically, from the blood into the intestinal lumen. Clinical and experimental evidence is presented below to show that this large outflow of alkali is dependent, to a great degree, on the large inflow of alkali into the blood, at the level of the parietal cells of the stomach (Table 1).

TABLE 2 :—*Normal Daily Turnover of Gastrointestinal Secretions in Average Adults with Certain Important Values.*

| Secretion | Volume ml./24 hr. Average | Range | pH Range | Bicarbonate content mEq./L |
|---|---|---|---|---|
| Saliva ... | 1500 | 500—1500 | 6.0 — 7.1 | 10—15 |
| Gastric juice ... | 2500 | 1000—5000 | 1.0 — 3.0 | 0—14 |
| Pancreatic juice ... | 700 | 700—1000 | 8.4 | 121 |
| Bile ... | 500 | 100—1000 | 7.0 — 8.0 | 40 |
| Intestinal juice ... | 3000 | 700—3000 | 7.5 — 7.7 | 31 |
| Total | 8200 | 3000—11,500 | | |

Compiled from Atkinson[1], Weisberg[36] and Wright[40]

*Clinical evidence:*

A. Considerable modification of the pancreatic response to food follows gastrectomy[6]. There is a marked reduction in the volume, the bicarbonate concentration and the enzyme content[6]. Lundh[28] and Duthie[19] have reported reduced and delayed appearance of biliary and pancreatic secretions. Some of the pancreatic enzymes may be totally absent. Similar phenomena may follow vagotomy[11],[39].

The probable explanation is as follows:

All along the digestive tract, the output of enzymes occurs, hand in hand, with either an acid (HCl) or an alkali ($NaHCO_3$). A disturbance in the outflow of one (*i.e.* the alkali) leads to the disturbance in the outflow of the other (*i.e.* the P.I.B. enzymes). With HCl secretion by the stomach diminished or completely absent following gastrectomy, or vagotomy, there is no longer created the initial, vital "positive alkali balance" in the blood, which could have permitted the outflow of alkaline P.I.B. juices.

B. In most patients with duodenal ulcer, the pain occurs $1\frac{1}{2}$—2 hours after food.[2] At this stage, the stomach contains sufficient quantity of food.[5] Some of the chyme, however, that has entered the duodenum excites an outflow of alkaline P.I.B. juices. This necessitates an outflow of HCl and leads to gastro-duodenal irritation and pain.

*Experimental evidence:*

A. Cummins *et al.*[12] observed in their experiments on dogs that severe acidosis and duodenal ulcers occurred when HCl in physiologic concentration (0.16 N) was dripped into the stomach. If, however, 0.16 N $NaHCO_3$ (physiologic concentration) was introduced simultaneously, either into the intestinal lumen or intravenously, in corresponding quantities, neither acidosis nor ulcers occurred. Cummins *et al.*[12] could not explain these findings. The chain postulated above (Table I) explains them fairly clearly. When exogenous HCl alone was dripped, it failed to evoke the positive alkaline tide in the blood. When $NaHCO_3$ was given intraluminally, it mimicked the natural outflow of P.I.B. secretions. When $NaHCO_3$ was given intravenously, it mimicked the positive alkaline tide in the blood, thus permitting an outflow of the alkaline P.I.B. secretions, which combated the acid present in the digestive tract.

B. Rene[31] expresses surprise at the experimental severe hyperchlorhydria observed if the biliary and pancreatic juices are diverted to the exterior. The explanation is that if the gastro-intestinal tract loses large quantities of alkali to the exterior, the stomach must lose equally large quantity of acid, fortifying at the same time, alkali reserve of the blood.

C. Reference to Table 3 arouses interesting correlations.

TABLE 3 :—*Pancreatic Function and HCl Secretion.*

| | Experiment | Result | Explanation (by present authors) |
|---|---|---|---|
| 1. | Pancreatectomy[35] | Duodenal ulcer rare | Poor HCl secretion since need for alkaline tide in blood is diminished |
| 2. | Total pancreatic fistula[35] | Duodenal ulcer in 100% animals | Vide experimental evidence B. above. |
| 3. | Chronic pancreatitis[41] (in humans) | Duodenal ulcer rare | As in 1 above. |

IV. Endothermic reaction[21] and evolution of $CO_2$[35,40]:

A. Endothermic reaction:

$HCl + NaHCO_3 \rightarrow NaCl + H_2O + CO_2$ (Loss of Heat)

The endothermic reaction, probably serves as a thermostat. A reversible destruction of digestive enzymes occurs at higher temperatures.[16] It is possible that the endothermic reaction tends to keep the intraluminal temperature optimally low, so as to prevent undue inactivation of the enzymes.

B. Evolution of $CO_2$:

The small intestine is the *raison d'être* of the digestive tract, the essential digestion taking place only there[1,15]. It is here that HCl and $NaHCO_3$, mixing intimately with food, react with each other, releasing $CO_2$. The evolution of $CO_2$ at the interface between the food and P.I.B. enzymes helps in fragmenting the food material, thus exposing a larger area of the substrate to the enzymes.

It would not be out of place here to deliberate on the importance of the juxtapositioning of a strong acid and a fairly strong alkali in the intestinal lumen. The only function ascribed to the acid and the alkali is the maintenance of an optimal pH. It should be realised, however, that if pH was the only problem, it could have been achieved with a very small quantity of acid and a correspondingly small quantity of alkali. Reference to Table 2 shows that the amounts of acid and alkali secreted, along with the digestive enzymes, are so large that they can be expected to have functions other than maintenance of pH. Dixon[16] has emphasised the specific role of cations Na and K + in the activation of various enzymes. Summarising, one can say that apart from partaking in maintenance of pH, the outflow of acid and alkali, into the digestive tract provides—(i) endothermic reaction, (ii) release of $CO_2$, (iii) cations —all the three being salutory to the action of enzymes.

**Basal versus Augmented Phase of Gastric HCl Secretion:**

The lumen of the digestive tract is a temporary physiological exile for the acid and alkali of the body[26] (Diagrams 2 and 4). A large quantity of acid or alkali can be voided into it, to adjust the pH of the blood. Clinical and experimental evidence supporting the above concept has been presented elsewhere[26].

That the HCI secretion by the stomach is not only a continuous process but also a vigorous one, has been accepted[1,14,20,35]. As suggested in the comparison between the stomach and the lungs in the earlier part of this article, it is proposed that under basal conditions, onto the parietal cells of the stomach, falls a constant load of acid-elimination, resulting in continuous HCI secretion. This could be called the basal, the continuous, the resting or the unaugmented phase of HCI secretion. The further fate of this secretion is discussed elsewhere[26].

In contrast to the basal phase, we suggest the presence of the augmented phase of gastric HCl secretion. This phase could be divided into—(a) The digestive augmented phase, and (b) the metabolic or the non-digestive augmented phase.

The digestive augmented phase permits a positive alkaline tide in the blood, thereby facilitating the outflow of alkaline digestive juices The metabolic augmented phase takes care of any acid load on the circulating blood (metabolic acidosis). Evidence has

been presented to show how the stomach partakes in the management of any acid load on the blood[26]. Two common examples should suffice at the moment. Surprise has been expressed at the hyperchlorhydria, in starvation and during sleep[1,17,35]. If it is realised that both in starvation and sleep, there is a state of metabolic acidosis or ketosis[36], the hypersecretion of HCl by the stomach would not remain a matter of surprise.

SUMMARY

A new concept of the role of HCl secretion by the stomach has been presented. It has been described how the stomach by its secretion of HCl partakes in acid-base regulation and also contributes vitally to the enzymatic apparatus in the digestive tract.

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been presented to show how the stomach partakes in the management of any acid load on the blood[26]. Two common examples should suffice at the moment. Surprise has been expressed at the hyperchlorhydria, in starvation and during sleep[1,17,35]. If it is realised that both in starvation and sleep, there is a state of metabolic acidosis or ketosis[36], the hypersecretion of HCl by the stomach would not remain a matter of surprise.

SUMMARY

A new concept of the role of HCl secretion by the stomach has been presented. It has been described how the stomach by its secretion of HCl partakes in acid-base regulation and also contributes vitally to the enzymatic apparatus in the digestive tract.

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# Reduction of gastric acid secretion on a low-salt diet and furosemide

M. L. KOTHARI, J. C. DOSHI, H. G. DESAI, A. B. VAIDYA, U. K. SHETH, AND J. M. MEHTA

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# Reduction of gastric acid secretion on a low-salt diet and furosemide

M. L. KOTHARI[1], J. C. DOSHI, H. G. DESAI, A. B. VAIDYA, U. K. SHETH, AND J. M. MEHTA

*From the Department of Clinical Pharmacology, Seth G.S. Medical College, the Department of Medicine, K.E.M. Hospital, and the Department of Gastroenterology, Bai Yamunabai L. Nair Charitable Hospital, Bombay, India*

The management of peptic ulcer essentially consists of the neutralization or the reduction of gastric hydrochloric acid (HCl) by the use of antacids, anticholinergics, or by surgery. The drugs are partially effective, and surgery, with its known hazards, has a limited application. Johnston (1965), in a review of the various medical methods for the reduction of gastric acid secretion, concluded that none was satisfactory. An accidental observation of the relief of symptoms of duodenal ulcer in a patient while on a low-salt diet, advised for a different reason, prompted the present study.

## MATERIAL AND METHODS

Twelve patients with active duodenal ulcer and six healthy controls, a total of 18 subjects, were studied. Seventeen were males and one female. The gastric secretory response was studied either by the augmented histamine test (AHT) (Kay, 1953) or by the histamine infusion test (HIT) (Lawrie, Smith, and Forrest, 1964; Desai, Borkar, and Jeejeebhoy, 1967). In overnight fasting subjects, a 14 to 16 French Levine tube was passed under fluoroscopic control along the greater curvature of the stomach with the tip of the tube placed at the right border of the vertebral column. The patients were instructed to lie on the left side and not to swallow saliva during the period of collection. The gastric secretion was collected by intermittent hand suction. After aspirating the fasting contents, 50 mg mepyramine maleate was injected intramuscularly and the basal secretion collected for half an hour. Histamine acid phosphate was then injected subcutaneously (AHT) or given in an infusion of 5% glucose (HIT). In the AHT the collection of gastric secretion was done for one hour after the injection of histamine. In the HIT, four 15-minute samples were collected after a 'steady state' was reached and pooled. The total acidity in the gastric samples was titrated against freshly prepared N/10 NaOH using phenolpthalein as the indicator and expressed as m-equivalents per hour of HCl (Lawrie and Forrest, 1965; Desai *et al*, 1967).

In the first group of seven subjects (Table I), the acid output was measured, on admission, by the AHT (histamine 0·04 mg/kg body weight). The test was repeated after a period of nine to 20 weeks (mean period = 14 weeks) on a low-salt diet. A low-salt diet meant the avoidance of common salt (NaCl) in food. No other dietary restrictions were imposed and no drugs prescribed. In subject no. 1 (control), the acid output was measured on six occasions, before and after maintenance on a low-salt diet, with an interval of 15 days between two successive tests. In the second group of 11 subjects, the HCl output was measured, on admission, by the HIT (histamine 0·04 mg/kg body weight/hour in subjects weighing more than 50 kg and a dose of 2·0 mg/hour in

[1]Please address requests for reprints to Dr Kothari, at the Department of Clinical Pharmacology, Seth G.S. Medical College, Parel, Bombay 12

TABLE I

GASTRIC ACID OUTPUT (AHT) BEFORE AND AFTER LOW-SALT DIET

| *No.* | *Age (yr)* | *Subject* | *HCl (m-equiv/hr)* | | |
|---|---|---|---|---|---|
| | | | *On Admission* | *After Salt Depletion* | *Difference* |
| 1 | 30 | Control | 43·81[1] | 27·7[1] | −16·1 |
| 2 | 24 | Duodenal ulcer | 53·0 | 21·2 | −31·8 |
| 3 | 36 | Duodenal ulcer | 28·4 | 22·8 | − 5·6 |
| 4 | 40 | Duodenal ulcer | 36·9 | 33·5 | − 3·4 |
| 5 | 50 | Duodenal ulcer | 41·8 | 18·7 | −23·1 |
| 6 | 54 | Duodenal ulcer | 29·8 | 24·6 | − 5·2 |
| 7 | 54 | Duodenal ulcer | 17·41 | 15·41 | − 2·0 |

$t = 2{\cdot}870$ $df = 6$ $P < 0{\cdot}05$

[1]Average of six serial tests.

All subjects were males.

TABLE II

GASTRIC ACID OUTPUT (HIT) BEFORE AND AFTER FUROSEMIDE

| *No.* | *Age (yr)* | *Subject* | *HCl (m-equiv/hr)* | | |
|---|---|---|---|---|---|
| | | | *On Admission* | *After Salt Depletion* | *Difference* |
| 1 | 22 | Control | 31·1 | 28·2 | − 2·9 |
| 2 | 25 | Control | 25·6 | 21·0 | − 4·6 |
| 3 | 30 | Control | 16·2 | 18·2 | + 2·0 |
| 4 | 45 | Control | 15·4 | 12·4 | − 3·4 |
| 5 | 35 | Control | 17·0 | 9·9 | − 7·1 |
| 6 | 39 | Duodenal ulcer | 25·7 | 16·3 | − 9·0 |
| 7 | 30 | Duodenal ulcer | 29·0 | 18·0 | −11·9 |
| 8 | 36 | Duodenal ulcer | 25·4 | 32·3 | + 6·9 |
| 9 | 45 | Duodenal ulcer | 43·0 | 24·2 | −18·8 |
| 10 | 40 | Duodenal ulcer | 15·0 | 4·8 | −10·2 |
| 11 | 30 | Duodenal ulcer | 43·2 | 31·4 | −11·8 |

$t = 3{\cdot}0$ $df = 10$ $P < 0{\cdot}02$
All males except case 1.

TABLE III

GASTRIC ACID OUTPUT IN SIX SERIAL TESTS (AHT) BEFORE AND AFTER SALT DEPLETION IN CASE 1

| *No.* | *HCl (m-equiv/hr)* | |
|---|---|---|
| | *On Admission* | *After Salt Depletion* |
| 1 | 43·0 | 28·4 |
| 2 | 43·8 | 28·0 |
| 3 | 44·1 | 26·9 |
| 4 | 44·3 | 27·3 |
| 5 | 43·4 | 28·2 |
| 6 | 44·2 | 27·4 |
| Average | 43·81 | 27·7 |

those weighing less than 50 kg). Thereafter, furosemide was administered orally in the dosage of 40 mg twice daily for a period of 10 days. The subjects were on a low-salt diet during the same period. Sixteen to 24 hours after the last dose of furosemide, the HIT was repeated.

## RESULTS

Table I shows the HCl output on histamine stimulation (AHT) before and after a low-salt diet. All the seven subjects showed a significant fall in output of HCl ($P < 0{\cdot}05$). Table II shows the HCl output (HIT) before and after furosemide. Nine of the 11 subjects showed a significant fall in the acid output ($P < 0{\cdot}02$). In subjects in whom the tests were repeated in order to judge the reproducibility of the results, the mean and SD of the differences of acid output in two tests were $0{\cdot}11 \pm 0{\cdot}98$ m-equiv/hr on AHT and $1{\cdot}1 \pm 0{\cdot}56$ m-equiv/hr on HIT (Desai *et al*, 1967).

## DISCUSSION

A significant reduction in the gastric acid output was observed with a low-salt diet alone and in combination with furosemide in 16 out of 18 subjects. This observation may provide a new approach in the management of peptic ulcer.

Taylor (1955) has mentioned that many years ago Kahn produced acid-free gastric juice in animals by prolonged feeding with chloride-free meat. Lahiri (1953) showed a fall in gastric HCl output on a low-salt diet. The possible mechanisms underlying the reduction of HCl secretion, observed in the present study, may be as follows:

1 The formation of HCl by the parietal cells involves the following reaction (Hightower, 1966):

$$NaCl + H_2O + CO_2 \rightleftharpoons HCl + NaHCO_3$$

According to the law of mass action, the reduction in the availability of NaCl, one of the reacting masses, can decrease the speed of forward reaction and hence diminish HCl production. A significant rise in basal HCl secretion has been observed in man after intravenous infusions of normal saline (Barreras and Donaldson, 1967). This shows that an increase in the availability of NaCl, the ultimate source of the chloride ion for HCl formation (Hightower, 1966), can step up the speed of the reaction and increase the production of HCl.

2 Salt withdrawal has been shown to increase the circulating levels of aldosterone in man (Leutscher and Axelrad, 1954; Crabbé, Reddy Ross, and Thorn, 1958; Bledsoe, Island, and Liddle, 1966) and animals (Binnion, Davis, Brown, and Olichney, 1965; Cade and Perenich, 1965). This may act at the level of the parietal cell, altering the rates of ionic transfer and thus depress the formation of HCl. Van Buchem, Doorenbos, and Elings (1956) observed histamine-fast achlorhydria in a patient with primary aldosteronism (Conn's syndrome). Following the removal of the tumour, the patient showed a very high level of HCl secreted.

Inhibition of carbonic anhydrase has been postulated as a mechanism for the reduction of HCl secretion by the stomach on the administration of diuretics such as acetazolamide or chlorothiazide in man (Kramer and Markarian, 1959; Lindner,

Cohen, Dreiling, and Janowitz, 1962) and animals (Ojha and Ahmed, 1967). In the present study, the last dose of furosemide was administered orally 16 to 24 hours before the HIT, by which time it is known to lose its activity (Robson, Kerr, Aschcroft, and Teasdale, 1964). Moreover, furosemide has been shown to have no effect on carbonic anhydrase (Muschaweck and Hajdú, 1964). It is felt that furosemide exerts its action through depletion of sodium chloride.

## SUMMARY

A significant reduction in the histamine-stimulated gastric acid output was observed with a low-salt diet alone or in combination with the diuretic furosemide in 16 out of 18 subjects. This observation may afford a new approach in the management of peptic ulcer.

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# A UNIFYING CONCEPT OF AGING, SENESCENCE (Cancer, Blood Vessel Disease, Diabetes Mellitus and Altered Cell-Immunocyte Interaction*) AND DEATH IN MAN**

M. L. KOTHARI AND LOPA A. MEHTA

"Nature red in tooth and claw sees to it that in the wild most individuals fall to predators when they are young and inexperienced or as soon as their physical faculties of strength and cunning begin to decline. In contrast, man and laboratory animals live a relatively sheltered life and are preserved to enjoy an old age. Death comes as a result of degenerative or malignant disease". (Loutit).[32] Amongst all animal species, man exhibits the widest spectrum of degenerative senescent processes and the present article aims at elaborating these as they occur in man. As all the vertebrates are constructed on a common general plan,[18, 34, 42] the processes detailed here for man would be applicable to other vertebrate species as well.

Biologists have been obsessed with elaborating those forces of Nature and Natural Selection which create life, make it grow and maintain it in health.[14, 18, 22 35]. There is, however, an unintelligent refusal[5] to appreciate and accept those forces of Nature which operate from within*** organism to bring about senescence and thereby terminate the life of the organism. As we see a positive plan in human embryogenesis and growth, we might as well look at senescent processes as programmed events, designed to terminate the life of an organism at a specified time. It is rather sobering to note that biologists have come to accept the finiteness of the lifespan of all the animal species, including the longest lived animal, the man.[6, 7, 8, 12, 22] In the next 10 years, human lifespan is unlikely to be extended by more than 30 days.

The present communication aims to draw generalizations regarding the four main senescent processes—Cancer, Blood Vessel Disease (BVD), Diabetes mellitus (Dm) and Altered Cell-Immunocyte Interaction in man (ACII) (Table 1)

## DEFINITIONS

The various terms comprising the title of the article need to be defined for several reasons: Aging and senescence are often taken

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* Altered Cell-Immunocyte Interaction (ACII) is a better term in place of Autoimmune Disease (See later).

** The absence of diabetes mellitus as a natural disease in non-humans, *ipso facto*, restricts the consideration essentially to man.

From the Department of Anatomy, Seth G. S. Medical College, Parel, Bombay-12.

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*** Aristotle[1]: Life is the power of self-nourishment, and of independent growth and decay.

TABLE 1

A COMPARISON OF BLOOD VESSEL DISEASE, CANCER, DIABETES MELLITUS AND ALTERED CELL IMMUNOCYTE INTERACTION FROM PERSPECTIVE OF AGING AND SENESCENCE

| *Criterion* | *Blood Vessel Disease* | *Cancer* | *Diabetes Mellitus* | *Altered Cell Immunocyte Interaction* |
|---|---|---|---|---|
| **A. TEMPORAL.** | | | | |
| 1. Commencement | Streaks of atheroma noticeable at birth. | The march towards cancer starts after cytodifferentiation by 12th week of intra-uterine life. | Known to occur in neonates, Prediabetes, a part of diabetes begins at conception. | Starts at birth. |
| 2. Phases | Latent phase followed by manifest phase. May remain latent throughout life. | Latent phase followed by manifest phase. May remain latent throughout life. | Latent phase followed by manifest phase. May remain latent throughout life. | Latent phase followed by manifest phase. Most often remains latent throughout life. |
| 3. Time governed | Manifest phase is a function of biological time registered in the cytochron of the dividing cells. | Manifest phase is a function of biological time registered in the cytochron of the dividing cells | Manifest phase is a function of biological time registered in the cytochron of the dividing cells. | Manifest phase is a function of biological time registered in the cytochron of the dividing cells. |
| 4. Role of cytomorphosis. | Function of senescent stage (III) of dividing cells. | Function of stage (IV) of dividing cells. | Function of stage IV of atrophy or of stage (III) of dividing cells. | Function of stage (III) of dividing cells. |
| 5. Temporal advancement | By diet, obesity, stress. | By carcinogens. | By diet, obesity, stress, pregnancy. | By trauma, bacterial infection, viral infection, toxin. |
| 6. Increase with increasing of age. | Yes. | Yes. | Yes. | Yes. |
| 7. Relation to reproductive age. | Noticeable spurt in post reproductive phase. | Noticeable spurt in post reproductive phase. | Noticeable spurt in post reproductive phase. | Noticeable spurt in post reproductive phase. |

TABLE 1—Continued

| *Criterion* | *Blood Vessel Disease* | *Cancer* | *Diabetes Mellitus* | *Altered Cell Immunocyte Interaction* |
|---|---|---|---|---|
| B. GENERAL FEATURES | | | | |
| 1. Tissue affected | Supporting tissue complex; essentially intercellular involvement. | Supporting tissue complex. Intracellular involvement. Affects dividing cells. | Supporting tissue complex, essentially intercellular involvement. | Supporting tissue complex. Both intracellular and intercellular involvement (dividing cells). |
| 2. Intrinsic in origin. | Yes; part of biologic trajectory or genetic programming. | Yes; part of biologic trajectory or genetic programming. | Yes; part of biologic trajectory or genetic programming. | Yes; part of biologic trajectory or genetic programming. |
| 3. Involvement of multiple systems. | Generalised process, death usually due to lethal occlusion in one particular region. | Involves one system; metastases involve multiple systems. | Generalised process; metabolic disturbances in addition. | Generalised process. |
| 4. Degree of change. | Minimum to maximum. | Minimum to maximum. | Minimum to maximum; metabolic abnormality and angiopathy exhibit minimum to maximum changes independent of each other. | Minimum to maximum. |
| 5. Occurrence in the young. | Single but severe senescent process | Single-usually the cause of death. Therefore senescent disease in children. | Single but severe senescent process. | Single but severe senescent process. |
| 6. % contribution to senescence. | By its universal distribution contributes maximum to process of senescence. | Contributes, but less than B.V.D. | Accelerates BVD. | Minimal direct contribution. Promotes or initiates BVD, Dm. |

TABLE 1—Continued

| *Criterion* | *Blood Vessel Disease* | *Cancer* | *Diabetes Mellitus* | *Altered Cell Immunocyte Interaction* |
|---|---|---|---|---|
| 7. Contribution to death. | Usually fatal. | Usually fatal. | Fatal through BVD. | Minimal except when as a manifest process in the young. |
| 8. Ontogenic effect | Blockage of 'life line' to cells with loss of nutrition. | Blockage of supply or exit lines; toxaemia of cancer; eventual loss of cellular nutrition. | Blockage of 'life line' with disturbed enzymatic machinery. | Contributes to cell loss, BVD., Dm. |
| 9. Species-Specificity. | Yes; highest incidence in man. | Yes; highest incidence in man. | Exclusive to man. | Exclusive to vertebrates. |
| 10. Biologic Significance. | Inexorable expression of cell's ability to 'destroy'; part of 'Nature red, in tooth and claw'. | Inexorable expression of cell's ability to 'destroy'; part of 'Nature red in tooth and claw'. | Inexorable expression of cell's ability to 'destroy'; part of 'Nature red in tooth and claw'. | Inexorable expression of cell's ability to 'destroy'; part of 'Nature red in tooth and claw'. |
| 11. Co-senescent Processes. | Often coexists with cancer, Dm & ACII in the same individual. | Often co-exists with BVD, Dm. | Accelerated BVD is part of Dm. ACII probably its cause. Cancer may co-exist. | ACII plays some role in the genesis of BVD and Dm. It is unable to check cancer though it may co-exist. |
| 12. Spontaneity. | Yes. | Yes. | Yes. | Yes. |
| 13. Universality. | Universal disease of mankind; can be induced in animals, spontaneous incidence in animals significant. | Universal disease of mankind; universal distribution in the animal & plant kingdom. | Universal but exclusive to mankind; can be induced in animals. | Universal disease of mankind. Can be induced in animals. |
| 14. Progressiveness | Yes. | Yes. | Yes. | Yes. |
| 15. Deleteriousness | Yes. | Yes. | Yes. | Yes. |
| 16. Irreversibility. | Yes. | Yes. | Yes. | Yes. |

TABLE 1—Continued

| *Criterion* | *Blood Vessel Disease* | *Cancer* | *Diabetes Mellitus* | *Altered Cell Immunocyte Interaction* |
|---|---|---|---|---|
| C. HEREDOFAMILIAL ASPECTS | | | | |
| 1. Role | Heredofamilial. | Many cancers are now shown as familial; clear evidence of hereditary transmission in only 4-6 types of cancers. | Heredofamilial. | Familial (e.g. SLE, Hashimoto's disease). Role of heredity is being increasingly established. |
| 2. Mode of inheritance. | Multifactorial inheritance. | Multifactorial inheritance. Autosomal recessive gene for clearly inherited cancers. Presence of facultative cancer genome prerequisite in tissue affected. | Recessive gene; concurrent gene mediating angiopathy; 6% of the population is homozygous for these genes. | Not known. Occurrence in twins suggests genetic predisposition. |

as synonymous despite inherent differences. BVD and ACII are introduced as new terms, new concepts. Cancer and Dm[21, 22, 23, 24, 26] have been described here, and in earlier communications, as senescent processes. The culminating event, Death, is dealt with at the end after the various senescent processes have been defined, corelated and imparted a temporal dimension. Each of the senescent processes has been described in detail in separate publications.

**Aging:-** Aging* is the time-journey executed by the organism since its ontogeny and could be considered either from the time of conception or birth.[12, 37, 39] It is strictly a calendar of physical time on which the biological events of birth, growth, reproduction, senescene and ultimately death are charted. Aging has effects both favourable (positive) and deleterious (negative) upon the organism. To cite the favourable ones: dentition, growth, acquisition of immunity. The examples of negative aging are too well known to be cited here. It is unfortunate that the term aging is used to mean physical deterioration with passage of time. The term aging should be reserved for the organism as a whole, as a chronological relation in its development and ontogeny. (Yemm).[46]

**Biological Aging:-** Biological aging is the passage of biological time measured in terms of the occurrence of a set of biological events or calendar events. As yet no suitable calendar event for measuring biological time has been found. A major handicap is the fact that different systems in an individual show varying rates of biological aging despite the same chronological age. Cowdry[11] has stated that each cell in the body ages at its own rate. We have suggested that for measurement of biological aging in man, the palpable event of cell division be taken as the calendar event for that cell in particular and the organism in general. (It is obvious that non-dividing cells of the body cannot so contribute to the function of registering biological time). To give a suitable example: an individual has cells A and B, each with a total doubling capacity of 50 divisions. If cell A expends 25 divisions and B expends 10 divisions within the same chronological time t, the cell A has biologically aged $2\frac{1}{2}$ times more than the cell B. The individual is biologically young with regard to the cell B but old with regard to the cell A. Taking a grosser event into consideration, an individual with loss of teeth and/or greying of hair at age of 30 is biologically older, with regard to these two systems than another individual of 30 with full complement of teeth and absence of grey hair. However, the latter individual may be having coronary arteries which have biologically aged much more than those in the former individual who might easily outlive the latter.

**Senescence:-** Senescence is the manifest, structural and/or functional expression of the otherwise abstract phenomenon of biological or chronological aging and which increases the probability of death of the individual.

* Unless qualified, the terms aging and age refer to physical or chronological time only.

Comfort defines senescence as a deteriorative process, a later stage of the individual's development.[7, 8, 9, 10] It is the eventual outcome of the unidirectional[25] biological and chronological time-arrow and is comprised of progressive, deleterious and irreversible structural and/or functional changes affecting separately the cell, its surrounding interstitium, the blood vessels, the organs, the system and summatively, the individual, occurring at any age from time of conception of the individual to his death, as a result of a genetically coded programme of events *ab initio* in the life of the individual. Most of the cells, blood vessels, organs etc. of the individual exhibit synchronous senescence. However, amongst these there is usually a particular cell/s, blood vessel/s, organ/s etc. which because of predetermined short lifetime, exhibit advanced senescence while the counterparts elsewhere are relatively free from senescence. A child dying of leukaemia exhibits early senescence of the leukopoietic tissue and the same early senescence occurs in the coronary vessel in a young man dying of coronary occlusion. This varying rate of senescence in different areas of an individual's body accounts for the fact that most senile individuals possess almost the whole spectrum of senescent processes one of which is sufficiently advanced to kill him (with the aid of other senescent processes) so as to allure us, into stating, rather illogically, that so and so died of, say, carcinoma of stomach.

**Cancer:-** Cancer is an eventual, normal phase in the lifecycle of a dividing cell, *in vivo* and *in vitro,* provided the cell possesses the cancer genome. A cellular clock, the cytochron, governs the time of expression of the neoplastic potential of the cell. A carcinogen does not cause cancer but merely advances in time the occurrence of cancer.[21, 22, 23, 24]

**Blood Vessel Disease** (BVD):- This generic term, appears preferable to, and includes such specific processes as atherosclerosis, arteriosclerosis, arteriolosclerosis, capillaritis, endarterites obliterans and phlebosclerosis, all of which can occur, and often do occur, in the huge vascular tree of a senile individual whereby, because of vaso-occlusion and vaso-sclerosis, there is progressive loss of tissue perfusion and increasing peripheral resistance (causing systemic arterial hypertension*) which eventually lead to lethal vasculo-cerebral, vasculo-cardiac, vasculo-renal diseases and/or progressive heart failure because of hypertension. In a significant percentage (5-10%) of population, the process of BVD is accelerated by the presence of the syndrome of Dm.[26]

**Diabetes Mellitus (Dm):-** "The syndrome of diabetes mellitus consists of a genetically determined, universal, multiform, vaso-occlusive disease,

* Systemic arterial hypertension predominates because of the larger size of the systemic arterial tree as well as its greater involvement by both occlusion and sclerosis. Natural Selection has spared the pulmonary vascular tree from hypertension probably because of a significant contribution of the lungs to overall senescene by way of chronic infections, entrapping of inhaled particles, and neoplasms.

positively catalysed by another hereditarily transmitted trait of silent or manifest metabolic defects, particularly of carbohydrate metabolism. Both the genetic traits tend to exhibit maximal to minimal penetrance. The individual is eventually destroyed by some vaso-occlusion."[26]

**Altered Cell Immunocyte Interaction (ACII):-** The term "auto-immune disease" is innately wrong. The fundamental underlying mechanism is subserved by the increasing immunogenetic diversification of the dividing cell population of the body with increasing age resulting into progressively increasing "disturbed antigen" because of "somatic mutation" in the target cells and/or progressively increasing "disturbed tolerance" because of the mutation affecting the immunocytes of the body. This disorder of the interaction between the (target) cell and the immunocyte is best expressed as the Altered Cell-Immunocyte Interaction (ACII).[27]

**Iceberg Concept:-** (Fig. 1) At this stage one may recall the iceberg concept for the total quantum of disease processes in an individual. In a young individual, the iceberg consists of a single disease process: cancer, B.V.D., ACII or Dm. In an old individual the iceberg is made up of all these, with one of these processes forming the visible part of the iceberg. This analogy highlights another important biologic phenomenon. To terminate the life of a young individual, Nature employs a disease process, single but severe. In an old individual, many processes combine together to give

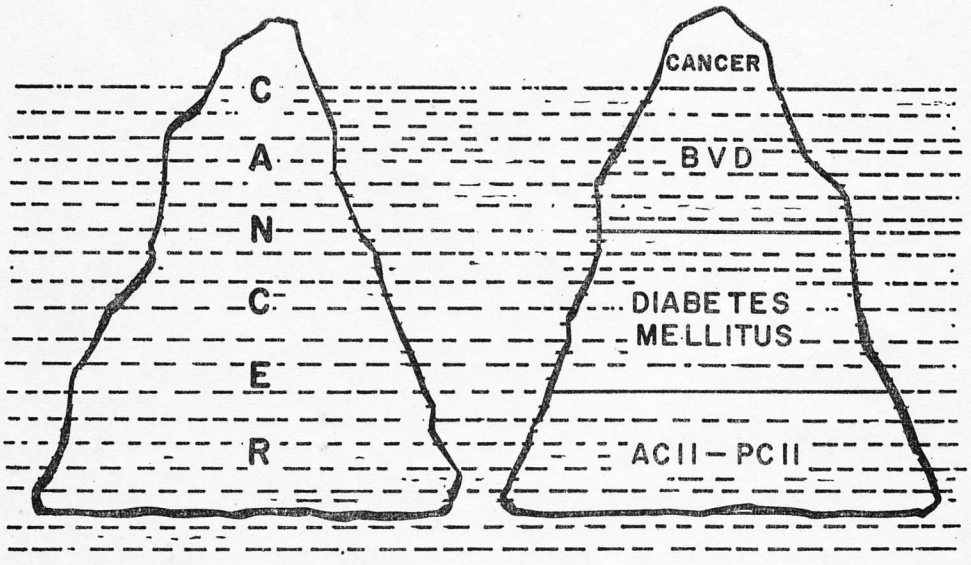


Fig. 1: The iceberg of lethal senescent process/es in a young individual (left) and an old individual (right).
ACII = Altered Cell-Immunocyte Interaction; PCII = Pathogenic Cell-Immunocyte Interaction

an effectively lethal iceberg. It would appear that even a senescent process blunts its edge with the aging of the individual.

## BASIC NEW CONCEPTS ON AGING AND SENESCENCE

1. Senescent processes, forming the intrinsic diseases, are a function of the aging of the organism and constitute part and parcel of the programmed biologic trajectory of the individual.

2. The four main senescent processes in man are Cancer, Blood Vessel Disease, Diabetes mellitus and Altered Cell-Immunocyte Interaction and these singly or together affect the supporting tissue complex (ST Complex).[22]

3. The whole spectrum of senescent processes has been evolved by Natural Selection as a means to terminate the life of the organism at a certain time so as to unfailingly subserve the finite life expectancy of the individual and the finite lifespan of the species.

4. These processes are not prerogratives of senile individuals. Their occurrence in younger individual tends to be single but severe.

5. All these phenomena are time governed and the type of senescent process and the time of its occurrence is determined by the interplay of stochastic (environmental) and genetic factors.

6. The phenomenon of increasing senescence with increasing age in the animal kingdom, and the plant kingdom is an inherent protoplasmic repertoire subserving the Gompertz phenomenon of increasing mortality with increasing age which, in turn, subserves the dynamics of bioecological balance.

7. The SNM Complex[22] composed of perennial cells does not partake in these senescent processes. However heredofamilial, time governed atrophic diseases involve one or more components of the SNM complex in a small group of individuals.

**Tissue Participants in Senescence:**—For all classes of vertebrates, Nature has employed a common plan of body construction[18, 34, 42] Typically, a vertebrate animal consists of the SNM Complex subserved by the Supporting Tissue Complex (Fig. 2).

The SNM Complex has somatic and visceral divisions and is comprised of the sensorium, the neuronium and the motorium formed by non-dividing, non-mitotic, perennial, sensory receptors, neurones and muscle cells. The S and N parts of the visceral SNM Complex are very small. The SNM Complex is subserved by the Supporting Tissue Complex (ST Complex) which consists of the rest of the tissues including the neuroglia and the endocrines. The ST Complex is constituted by dividing cells, expanding or renewing in their proliferative behaviour.[28, 29] The entire vascular tree is a part of the ST Complex. The intercellular substance, consisting of ground substance, elastic fibres, and collagen fibres is its important extracellular and extravascular

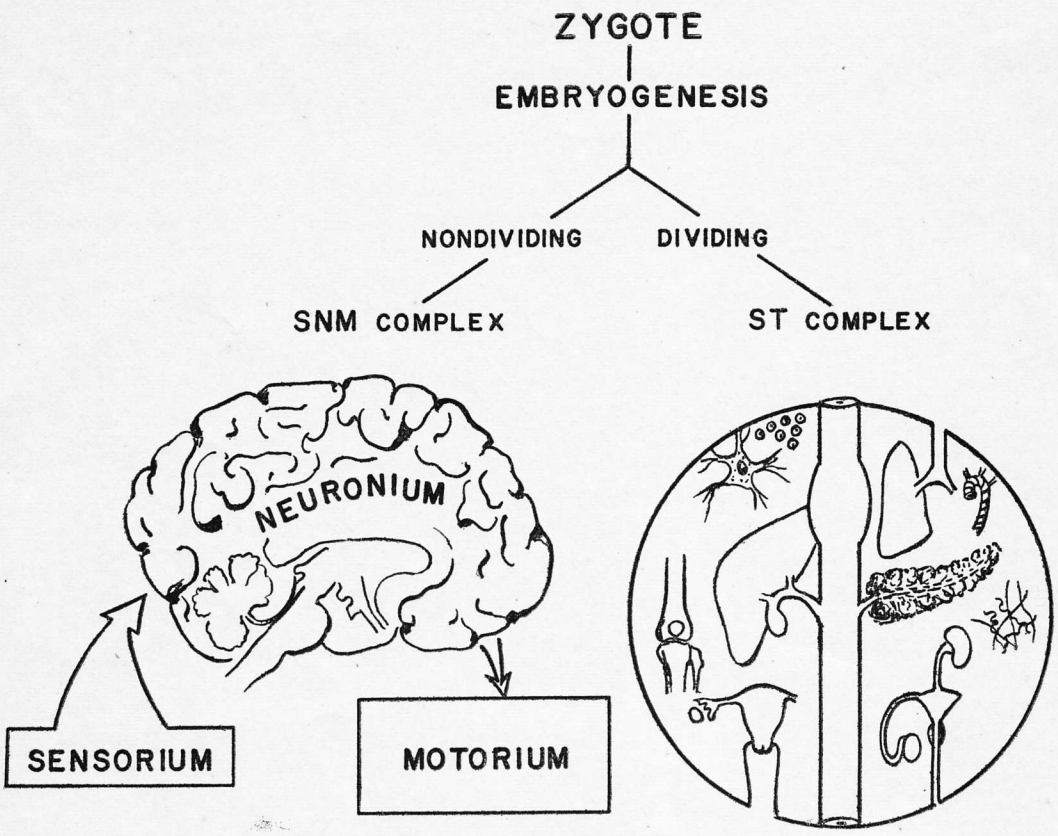


Fig. 2: The SNM vs. ST complexes.

element. The cellular expression of the finite lifespan of an animal species is to be found in the Finite Cell Doubling Capacity (FCDC) of the dividing cells in the ST Complex of the animal.[23]

**SNM Complex as Self and ST Complex as Not-Self:**

The SNM Complex constitutes the *raison detre* of a man's or an animal's existence. It is the repository of the organism's soul, the *modus operandi* of his cognitive, cerebrative and conative faculties, the basis of interspecies and even intraspecies variations, the heart of organic evolution, the immortal and the perennial within the mortal individual.[25] The SNM complex constitutes the SELF as against the NOT SELF constituted by the ST complex. SNM Complex exhibits immunity from cancer and ACII, both prerogatives of dividing cells only. Being perennial in nature, it is not primarily prone to atrophy* save as a result of such secondary factors as BVD. The above characteristics permit the statement that SNM Complex being SELF does not destroy the individual whose life is brought

* Except certain heredofamilial atrophic disorders.

to an end at a finite time by intrinsic processes affecting his NOT-SELF, the ST complex.

**Age Distribution of Senescence**

It is a fallacy to maintain that senescence is a prerogative of those who are advanced in age. Senescence has been defined as intrinsic, deleterious, progressive, irreversible changes in the cells and tissues, and which increases the probability of death of the individual. Now, a child dying of cancer dies of a senescent process. It died of a process that was intrinsic, deleterious, progressive, irreversible, and which when the child was alive had increased the probability of its death. Cancer is one senescent process that occurs at all ages. Such reasoning would apply to a young man/woman dying of 'premature' coronary occlusion or a form of ACII such as systemic lupus erythematosus.

**Senescence: Lethal/Non-Lethal**

Though senescence has been defined earlier as increasing the probability of death, a distinction needs to be drawn between such senescent processes and others which do not so contribute such as falling of teeth, greying of hairs, wrinkling of skin. It may be noted that the above processes are intrinsic, progressive, irreversible but their deleterious value is questionable. They may, however, be indicative of an underlying potentially lethal, senescent process.

An important, apparently non-lethal, time dependent senescent change is the affection of body's fiber systems, both collagen and elastic. It may be noted that the same cell, fibroblast, gives rise to collagen and elastic fibres. Collagen fibres exhibit increasing number of cross-links, diminution of water-content, increase in diameter and increase in tensile strength.[30, 31, 36, 38, 41] Alongwith these changes there is diminution of the mucopolysaccharide cement substance. The net effect is supposed to be a fall in the diffusibility of substances through the interstitium. Sobel,[36] however, after a critical analysis could conclude that no significant change in diffusibility, except some for oxygen, could be demonstrated. The elastic fibres show progressive fragmentation, loss of elasticity and calcification. The changes in the two fiber-systems probably play an important role in promoting the age-dependent BVD, by producing vaso-sclerosis because of the thickening of collagen fibres and the loss of elasticity of the elastic fibres, as well as by promoting vaso-occlusion because of the fragmented elastic fibres serving as the seat for deposition of atheromatous material.

**The Timing of Senescent Processes: The Cellular Timebomb**

The assumption that the senescent processes are preplanned *ab initio* makes it imperative to provide an intrinsic, cellular mechanism or clockwork which would time the occurrence of a particular senescent change

for that cell (and the tissue or the organ) in particular and the organism in general. Such a cellular clock, at the ontogenic level, serves as a time-bomb for heralding senescent processes initially and causing death eventually.

The whole story of biological evolution rests on the stellar role played by a dividing cell. Truly, it is the dividing cell which by its divisibility creates, grows and maintains, and destroys the organism. It is significant that both cancer and ACII are prerogatives of the dividing cells only.

It has been suggested that the very process of cell division as occurs in the life cycle of a dividing cell in a metazoic organism such as man, serves best as the calender event for recording the biological age of the organism and to initiate and control the various processes from conception to death. Such a dividing cell has finite doubling capacity (FCDC) which is specific for that species and which controls the various stages (cytomorphosis)[22] in the lifecycle of the dividing cell. The various stages are briefly outlined below.

Stage 1. Embryonal stage. The entry of the sperm into the ovum triggers off this stage characterised by extremely rapid cell divisions, accompanied, a little later, by progressive differentiation leading to the formation of the embryo, a miniature form of the adult human. Cytodifferentiation in almost all tissues is well established by this time. The cells of the SNM Complex assume their non-mitotic character as well as the full complement of their number. The subsequent intranatal growth and the postnatal growth period is entirely a function of dividing cells belonging to the ST Complex.

Stage 2. Stable, differentiated stage:- This stage extends from the beginning of the foetal stage of development (end of embryonal stage) till the death of the organism, and even beyond, for the cells of the organism cultivated *in vitro*. During this stage the cell exhibits high structural (karyotypic), functional and mitotic fidelity. The cell in this stage does not excite ACII.

Stage 3. Stage of senescence:- This stage appears when the FCDC of the cell is nearly exhausted. It is characterised by senescent changes of karyotypic abnormalities which lead to faulty protein synthesis and excite ACII. This is the stage of the so-called somatic mutation. During this stage such a cell with karyotypic abnormalities may establish a clone so as to excite accelerated ACII. Such a phenomenon is more likely in the case of an immunocyte entering stage 3 and establishing a clone.

Stage 4. Stage of atrophy or cancer. The senescent cell of stage 3 after completing its assigned number of stage 3 divisions, either atrophies or undergoes a cancerous change.

**FCDC Quantum of Somatic Cells**

Every individual short lived or long lived possesses cells with very

high FCDC and therefore a lifetime greater than the total life of the individual, as well as cells with a short lifetime because of a low FCDC quantum. This concept of "mini-to-maxi FCDC" accounts for the various biologic phenomena stated below:

1. Burch's[3] concept that a constant number of dividing, somatic cells are at risk of somatic mutation, as a function of age, from the first year of life onwards. Further, that the average somatic mutation rate must also be correspondingly constant throughout life for both the immunologically competent cells (immunocytes) and the non-competent cells (target cells).

2. Curtis's[12] concept of somatic mutation as the basis of aging as shown by the increasing chromosomal aberrations with increasing age.

3. Increasing levels of antiautobodies* with increasing age.

4. Increasing ACII, BVD and Dm with increasing age.

5. Progressive decline in cell number with increasing age.

6. Increasing incidence of cancer with increasing age.

7. And summatively, increasing mortality with increasing age—the Gompertz's phenomenon.[7, 8, 9, 10, 12, 37]

**Biological Clock and Senescent Processes:**—Cell division has been suggested as the most useful calender event for measuring the biological time in a metazoic animal such as man. The stages in the cytomorphosis of a dividing cell have already been outlined. The longest stage is the second stage of stable cytodifferentiation wherein the cell exhibits high structural, functional and mitotic fidelity. Even in an individual of over 100 years of age one can find many cells exhibiting this stage.

For every dividing cell the exhaustion of FCDC marks its entry into the third or the senescent stage. The cell shows chromosomal aberrations which are commonly interpreted as 'somatic mutations'. Besides functional impairment, the cell's abnormal chromosomal constitution leads to ACII which probably induces changes of BVD as well. The aggregate ACII or BVD is a function of number of cells in stage 3. This number also governs the occurrence and severity of Dm. It is interesting to note that BVD and Dm have been ascribed at least partly to ACII.

The fate open to a cell at the end of stage 3 is either cancer or atrophy. One of the reasons why these stages do not excite ACII is that the cell can do so only in stage 3.

**Is senescence a disease process?** A process or a set of processes that are intrinsic to any system is governed by an essentially intrinsically timed mechanism and which begins to operate from the very time the system comes into being, cannot justifiably be assigned appellations such as disease, decay, degeneration and alike.

Just as a certain fixed lifetime is inherent to any radioactive element

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* This is a term preferable to 'autoantibodies'.

and the same is 'spent' in a graduate manner till the element is 'dead', so is an organism which by spending itself gradually completes its biologic trajectory. The inherent nature of senescent processes is suggested by the following facts:

1. All the 4 processes of cancer, BVD, Dm and ACII are planned well in advance and the 'beginning' is made soon after birth or rather at the time of conception.

a. The march towards cancer starts with the very first cell division after cytodifferentiation is complete at the end of embryonic stage of development, i.e. 8th week IUL. The occurrence of foetal cancer is an evidence of a process sufficiently foreshortened and significant enough to indicate the initiation of such a process in other individuals where the neoplastic consummation may occur late in life.

b. Atheromatous streaks are evident in major arteries soon after birth. The changes in collagen and elastic fibres are noticeable.

c. The stage of prediabetes starts at the time of conception of that particular affected individual.

d. A 'constant' number of cells are at the risk of somatic mutation, and excite ACII from the first year of human life. (Burch)[3]

2. Each of the 4 processes (as well as their components) occur to a variable extent in almost every individual, given sufficient time for the individual to age.

a. The incidence of occult cancer of prostate tends to reach 100% in males in the 80-90 years age group. This phenomenon of silent cancers must be occurring at other sites as well.

b. Every individual is as 'old' as his arteries and this holds true for every artery in the body. Increase in B. P. is a function merely of the age of the individual.

c. Impaired glucose tolerance likewise is a function of age, even in non-diabetic individuals.

d. Antiautobodies can be demonstrated in every adult individual, normal or suffering from ACII. The level of the antiautobodies is a function of age.[43]

3. An immediate corollary of the above is the realisation that each of the senescent processes differs from one person to another by the degree or the quantity of it but not the quality nor the fundamental nature. Each of these processes therefore assumes a quantitative dominance and one particular process is too dominant in a certain individual so as to be immediately incriminated as the 'cause of death' of that individual. Sir George Pickering[33] has stated that essential hypertension is a quantitative disease. The same is true of the vagaries of HC1 secretion. The same is true of cancer, BVD, Dm and ACII.

4. Each of these processes prior to the manifest phase and even

thereafter is silent and often mild enough not to cause manifest disease in the affected individual.

a. Cancer, by the time it is manifest has sufficiently advanced in its course.

b. BVD of the most advanced nature may never let the individual feel its evolution or presence.

c. Prediabetes, latent diabetes and occasionally even manifest diabetes are symptomless.

d. The presence of high levels of antiautobodies is a normal occurrence (epiphenomenon) in aged individuals.[43]

These processes remind of a guest who has come to stay for many years but who, the moment he comes, books his return passage. The single most important quality of protoplasmic integration is 'decision in advance, of performance'.[17] The genetic set-up of the individual human being decides, *ab initio,* when he would and how he would depart. The spectrum of events in between is a necessary preparation for the departure.

**The raison detre of Senescence:—**

> Enlarge my life with multitude of days,
> in health, in sickness, thus the supplicant prays;
> Hides from himself his state, and shuns to know
> that life protracted is protracted woe.
>
> Samuel Johnson.[20]

Wallace's[44] conclusions, based on mathematical models, that senescence is inevitable in any system of living things leaves the pathos in the above line unmitigated. There has been considerable resistance against assigning a positive role to the process of senescence consequent on aging. While we admire Nature for all it creates and maintains we, because of the anthropocentric ego, are unable to assign role to this later part of the programmed trajectory of man. We have come to accept the finiteness of the lifespan of each animal species as well as that of the life expectancy of an individual of that species wherein life expectancy is never greater than the lifespan*. The evolutionary importance of this finiteness has

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* Lifespan has been defined as "the longest period over which the life of any plant or animal organism or species may extend, according to the available biological knowledge concerning it". (RHDEL)[40] Life expectancy is "the probable lifespan of an individual or class of persons determined statistically, affected by such factors as heredity, physical condition, nutrition, occupation, etc." (RHDEL).[40] Since the mortality rate in any human population increases progressively with increasing age of the population, life expectancy at the individual level as determined by the Gompertz phenomenon ranges from a few (3-5) years to the Vedic blessing of nearly 100 years. The high mortality in the first year after birth (mortality of transit from the safe dependent intra-uterine life to the hazardous independent extra-uterine life) rapidly decreases to reach the lowest value by 3-5 years of age after which it progressively increases as stated earlier.

already been elaborated. The Gompertz phenomenon operates from insects to man.[7, 8, 9, 10, 12, 16, 37] Finite lifespan and finite life expectancy, therefore, become natural functions of any living species where more and more individuals die with increasing age. The triple biologic function viz., finite lifespan, finite life expectancy and Gompertz phenomenon, can only be served by programmed senescence which should and does increase with increasing age, increasing thereby the probability of death and eventually death itself.

## DEATH

The body dies
Not I.
I, the soul eternal,
Live forever.
(Translated from a prayer)

The scramble for donors for heart transplants raised the important issue of defining the criteria by which an individual can be declared dead, once and for all. It is unfortunate that human death has not been adequately defined. The stanza quoted earlier inevitably raises the question as to what dies when a man dies.

**Self and Not-self in Man:**—Each man is his highly individual cognitive, cerebrative and conative SELF residing in his SNM complex and subserved and supported by the ST complex or his NOT-SELF. It is the lifetime of the latter that determines the life expectancy of the individual. Natural senescent processes wreck the ST complex so that both the self and the not-self come to an end. Such a situation satisfies the archaic signs of the cessation of vital functions of circulation and respiration as indicative of death. A necessary corollary, as yet unstated, is that these vital signs may be fully present and yet the individual, his self, may be dead. A decerebrate individual has lost his cognitive, cerebrative and conative faculties; his 'self is dead' although his 'not-self is alive' and may remain so as long as the lifetime of his ST complex. Hence, human death calls for two separate definitions.

1. Death of self:- This is said to have occurred when the individual suffers total, permanent and irreversible loss of his cognitive and conative faculties. With neither of these faculties present, cerebrative faculty *ipso facto* does not exist. Needless to say respiratory, circulatory, nutritive and excretory functions of such an individual may continue unabated for many years.

2. Complete death:- The cessation of function of both self and not-self signifies complete death. Since it is the self that depends entirely on the not-self and not *vice versa* and since it is in the very nature of the self or the SNM complex to be unable to survive beyond a few minutes without the supportive function of the not-self or the ST complex, all

natural deaths involve primarily the ST complex, wherein a complete irreversible break in one of its vital links wrecks the total ST complex and the complete individual.

**Modus operandi of Death due to Senescence** (Figs. 3, 4):—Although the data on the Gompertz phenomenon (Table 2) would frighteningly indi-

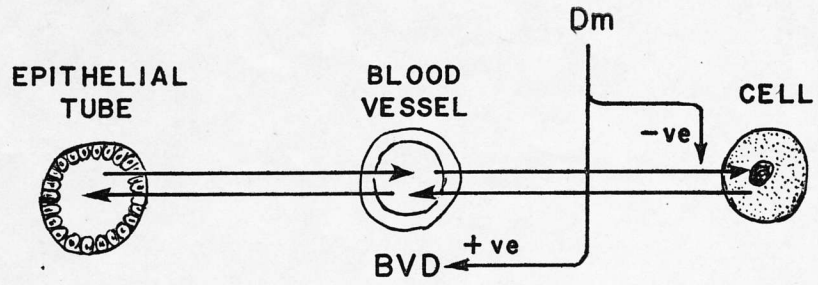
TABLE 2.

GOMPERTZ PHENOMENON.

(Increasing mortality with increasing age).

| | | |
|---|---|---|
| BASIS: | | |
| I. Cellular | | |
| With increasing age: | | |
| Increasing:— | i. | Loss of FCDC |
| | ii. | Chromosomal aberration |
| | iii. | Somatic mutation |
| | iv. | ACII |
| | v. | Loss of cell number |
| | vi. | Cancer. |
| II. Vascular. | | |
| With increasing age: | | |
| Increasing:— | i. | BVD |
| | ii. | Hyperpiesis. |
| III. Interstitial. | | |
| With increasing age: | | |
| Increasing:— | i. | Collagen thickening |
| | ii. | Loss of ground substance |
| | iii. | Decline of permeability |
| IV. Metabolic | | |
| With increasing age: | | |
| Increasing:— | i. | Serum lipids |
| | ii. | Decline of sugar tolerance |
| | iii. | Diabetes mellitus |
| V. Implications: | i. | An absolute, deterministic expression of increasing decline in protoplasmic vitality with increasing age |
| | ii. | Both intrinsic and extrinsic factors promoting death attack and kill individuals with vitality low enough for their age. |
| | iii. | Human beings, on the basis of a probability distribution, are intrinsically programmed to live for only a few years to nearly 100 years. Life expectancy is more a function of the life line on one's palms rather than the miracles of modern medicine. |

cate that every cell, fibre or blood vessel inexorably becomes senescent with age, it is not the aggregate senescence that precipitates the death of the individual. It is usually one organ or system forming but a small part of the vast STC, that fails in its obligatory function, thus leading to the failure of ST complex and finally to death. This concept has been entertainingly satirised by Oliver Wendell Holmes in his poem "The Deacon's Masterpiece" which we have titled differently.




| | | |
|---|---|---|
| CANCER | VASO-SCLEROSIS | NO CHANGE (Stage 2) |
| LEADING TO | VASO-OCCLUSION | SENESCENCE (Stage 3) |
| BLOCKAGE | HIGH B.P. | ACII (Stage 3) |
| OF | LEADING TO | ATROPHY (Stage 4) |
| NUTRITION | LOSS OF TISSUE- | CANCER (Stage 4) |
| RESPIRATION | -PERFUSION AND/OR | DISORDER OF |
| EXCRETION | CARDIAC FAILURE | CELL NUMBER, TYPE AND/OR POSITION |

Fig. 3: The involvement of epithelial tubes, blood vessels and cells as forms of senescence and causes of death.

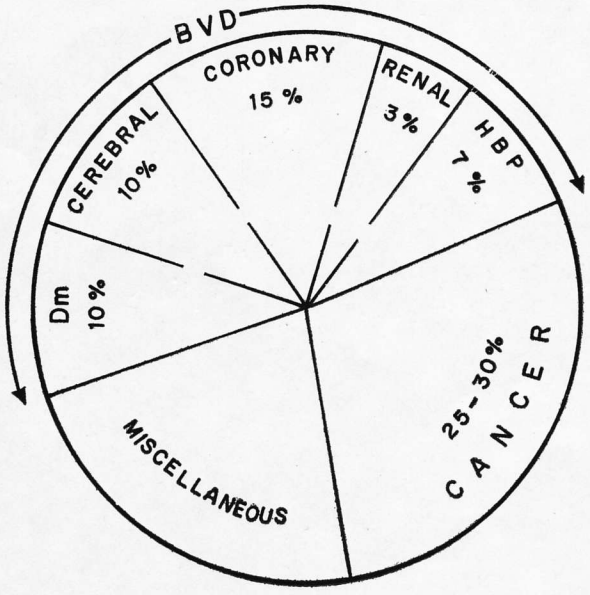



Fig. 4: The causes of death in an affluent well-cared-for society are grouped here along with their percentage contribution. Almost 30% of the deaths are due to vasculo-cerebral, vasculo-cardiac and vasculo-renal diseases. (The terms cerebrovascular, renovascular are operationally wrong for the primary involvement is of the vessels). Diabetes mellitus (Dm) usually kills through accelerated BVD. HBP = high blood pressure (systemic arterial).

WEAKEST LINK
OF EVERY INDIVIDUAL.
Now, in building of chaises, I tell you what,
There is always somewhere a weakest spot,-
In hub, tire, felloe, in spring or thill,
In panel, or crossbar, or floor, or sill,
In screw, bolt, thoroughbrace,—lurking still,
Find it somewhere you must and will—
Above or below, or within or without,—
And that's the reason, beyond a doubt,
That a chaise breaks down, but doesn't wear out.

**N. B.:** Removal of the weakest link makes one of the weaker links the weakest.

An individual is best depicted as shown in fig. 5.

Senescence involves one or more elements of the tripod* with an eventual impairment of one of them severe enough for the tripod to collapse.** Any extrinsic aid may postpone such a collapse; e.g. artificial kidney may take care of the excretory function while a cardiac transplant may postpone heart failure. The success of such measures is usually marred by the fact that the artificially substituted system is a smaller part of the large overall senescence. A young individual, with minimal overall senescence but finite localized senescence in the form of a cancer, may respond very well to operative removal because of the absence of immediately subsequent senescent foci. But an old man, with widespread senescence, will succumb to coronary occlusion which may follow soon after his cancer had been satisfactorily treated. It is interesting that Blaiberg's second heart obtained from a young woman and almost free from significant atherosclerosis at the time of transplant developed within one year after being with Blaiberg so much of atheroma, as was not present in Blaiberg's own first heart which was with him for over 52 years. The second heart was seat of intense ACII and this coincidence of ACII and atherosclerosis strongly suggests a relation between the two.

**Role of extrinsic factors:**—Sir Macfarlane Burnet[4] has classified diseases into extrinsic and intrinsic depending upon the aetiology. Degenerative diseases (senescent processes) are intrinsic. Extrinsic diseases include infections, nutritional deficiences or excesses, toxins, and trauma. With man constantly at interaction with the inanimate and animate environment, it is but natural that the Total Disease Status of any individual is an outcome of the interplay of the positive (e.g. active immunity) and negative (e.g. senescence) intrinsic factors as well as positive (adequate

* cf. Rene Dubos'[15] "Modern medicine—A three-legged stool".

** Depending on 'the cause of death', an individual may be placed in a particular necrotaxa[13,35] cf. concept of radiotaxa and neoplastic taxa.

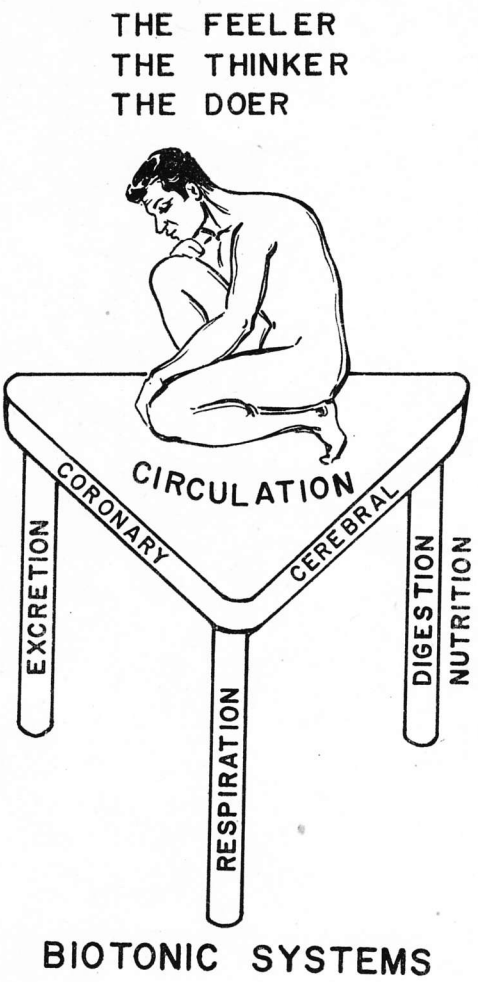



Fig. 5: The 'self' of the individual (SNM complex) rests on the ST complex (biotonic systems) whose universal feature is the blood vessels the involvement of which affects the rest of the ST complex as well as the SNM complex. It is usually the wreckage of the tripod (its top or one or more of its legs) by BVD, Cancer, Dm or ACII, that kills the individual.

nutrition, drugs) and negative (infections) extrinsic factors. There is an inherent fallacy in stating the cause of death such as, say pneumonia or cancer prostate. What actually leads us to stating such a definite cause of death is the iceberg phenomenon wherein the most visible part, pneumonia or cancer, may not have been the important one.

## DISCUSSION

In an age of computers, lunar landings and cardiac transplants, it tantamounts to commiting a heresy when one states that senescent processes

are programmed events, a normal part of the individual's development. The heresy further assumes a form of blasphemy when one states that the four main senescent processes outlined above are but a glimpse of the destructive or eliminative repertoire of the protoplasm. Successful euphenics* or some breakthrough in chemotherapy may cure mankind of one or more of above senescent processes. As and when that happens, Nature will unfold its sleeve to unleash other forms of senescent processes equally effective or even more so as to meet with the biologic requirement of finite life expectancy at the level of the individual and finite lifespan at the level of the species.

With the deciphering of the common universal genetic code reposited in DNA, and with the mounting evidence that from the level of viruses to that of man, all organisms use the same mechanisms for various cellular functions, that cytochrome C which has existed for $2 \times 10^9$ years and which is functionally and to a large extent structurally the same in yeast and man, one cannot but conclude with humility that all organisms are fundamentally alike. The gross resemblance of one vertebrate to another (study of man begins with study of frog) is an expression of a common plan of body-construction for all the vertebrates. We ought to have been surprised if we had failed to develop experimental atherosclerosis or cancer.

The morale of the above deliberation is that with the fundamental similarity of all living beings at the cellular level, we are unlikely to evolve a code which will selectively help us and not the sturdy cockroach, rat or the Staphylococcus aureus. All medical advances put together have not diminished the total number of diseases nor prolonged** the Biblical human lifespan of 3 scores and 10. It is in fairness of things that we develop a sense of biological neorealism and see a palpable plan in both embryogenesis leading to a live being and senescence which renders him dead.

## SUMMARY

It has been proposed and elaborated that Cancer, Blood Vessel Disease, Diabetes mellitus and Altered Cell-Immunocyte Interaction are intrinsic to man and other animals and are a result of a well defined programme whereby the individual is eliminated so as to serve certain principles of Natural Selection. It has been suggested that these processes are timed by the dividing cells of the body using their FCDC status as the guideline. All the four senescent processes bear a close comparison.

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* A term coined by Nobel Laureate Joshua Lederberg to mean the science of producing better phenotype by a fundamental alteration of the genotype.

** "Surprising as it may seem, life expectancy past the age of 45 is not increasing significantly anywhere in the world, not even among the social groups that can afford the most modern type of medical care" (Rene Dubos).[15]

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27

# THE NATURE OF DIABETES MELLITUS
## A POINT OF VIEW

**M.L. Kothari and Lopa A. Mehta**

*"The more we know about diabetes, the less we seem to understand it."* (*Boyd*)[17].

It has been increasingly realised that diabetes mellitus is a syndrome of multiple abnormalities[15,17,30,33,57,63] of which the abnormality of carbohydrate metabolism forms a subsidiary component.[30] The burden of the present communication is to view the Syndrome of Diabetes Mellitus in a larger perspective and thereby obtain a better understanding of it (Fig. 1).

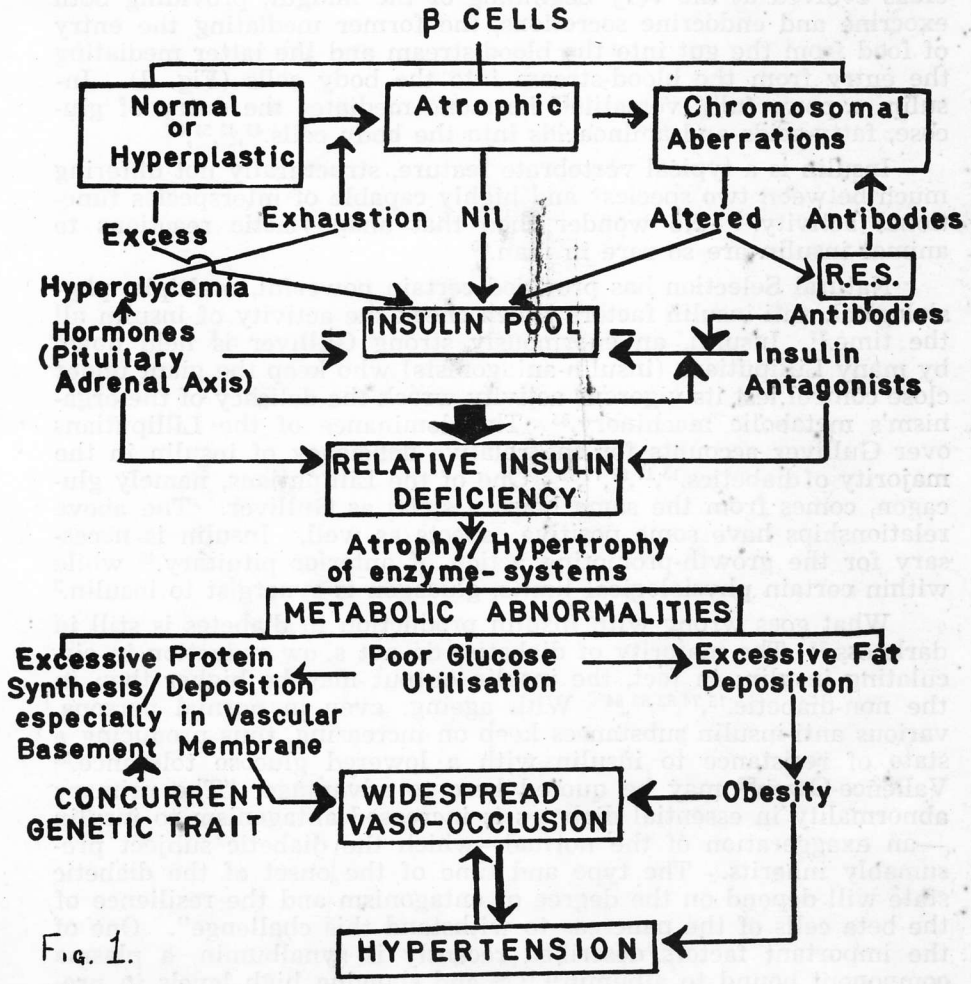


Fig. 1.

Department of Anatomy, Seth G. S. Medical College, Parel, Bombay-12.
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Just as Natural Selection[26,28,55,71] provides for growth and maintenance of various life forms, it, as well, invents mechanisms[44,45] which destroy the various organisms at varying stages of their life-spans. It is pleaded that the syndrome[57] of diabetes mellitus* is one such natural mechanism wherein an Accelerated[53] Vaso-Occlusive Disorder precedes, accompanies or follows a constellation of metabolic abnormalities due to a relative deficiency of insulin.[15,17,29,39,57,62,78,79] Such an unorthodox approach involves allusion to the evolution of the relevant positive (health-promoting) and negative (health-destroying) mechanisms of Natural Selection.

## EVOLUTION OF INSULIN

It has been emphasized that in the working of Natural Selection, functional necessity is the mother of structural innovation.[43] During the quantum biological jump from the invertebrate to the vertebrate stage, to provide a set of efficient fuel-pumps, the pancreas evolved at the very beginning of the midgut, providing both exocrine and endocrine secretions, the former mediating the entry of food from the gut into the blood-stream and the latter mediating the entry from the blood-stream into the body cells (Fig. 2). Insulin, a powerful,[85] versatile[57] hormone mediates the entry of glucose, fatty-acids and aminoacids into the body cells.[41,43,51,65]

Insulin is a typical vertebrate feature, structurally not differing much between two species† and highly capable of interspecies functional activity.[19] No wonder then that anaphylactic reactions to animal insulin are so rare in man.[60]

Natural Selection has provided certain powerful, multiple, physiological, anti-insulin factors which check the activity of insulin all the time.[77] Insulin, an enormously strong Gulliver is held down by many Lilliputians (insulin-antagonists) who keep the giant under close control lest its vigorous activity wreck the delicacy of the organism's metabolic machinery.[85] The dominance of the Lilliputians over Gulliver accounts for the relative deficiency of insulin in the majority of diabetics.[15,17,57,77,79] One of the Lilliputians, namely glucagon, comes from the same house (islets) as Gulliver. The above relationships have some positive aspects as well. Insulin is necessary for the growth-promoting action of anterior pituitary,[43] while within certain physiological limits, glucagon is synergist to insulin.[3]

What goes wrong with insulin production in diabetes is still in darkness.[85] The majority of diabetics do not show reduction in circulating insulin; in fact, the insulin output may be higher than in the non-diabetic.[15,74,82,83,84] With ageing, even in normal persons, various anti-insulin substances keep on increasing, thus producing a state of resistance to insulin with a lowered glucose tolerance.[39] Vallence-Owen[82] may be quoted here to advantage: "The primary abnormality in essential diabetes is increased antagonism to insulin —an exaggeration of the normal—which the diabetic subject presumably inherits. The type and time of the onset of the diabetic state will depend on the degree of antagonism and the resilience of the beta cells of the pancreas to withstand this challenge". One of the important factors described recently is synalbumin, a plasma component bound to albumin[41,77,82] and showing high levels in pre-

*Of the spontaneous variety, wherein the pancreas is neither evidently diseased nor surgically removed.

†Insulin-wise, man most closely resembles the pig.[83,85]

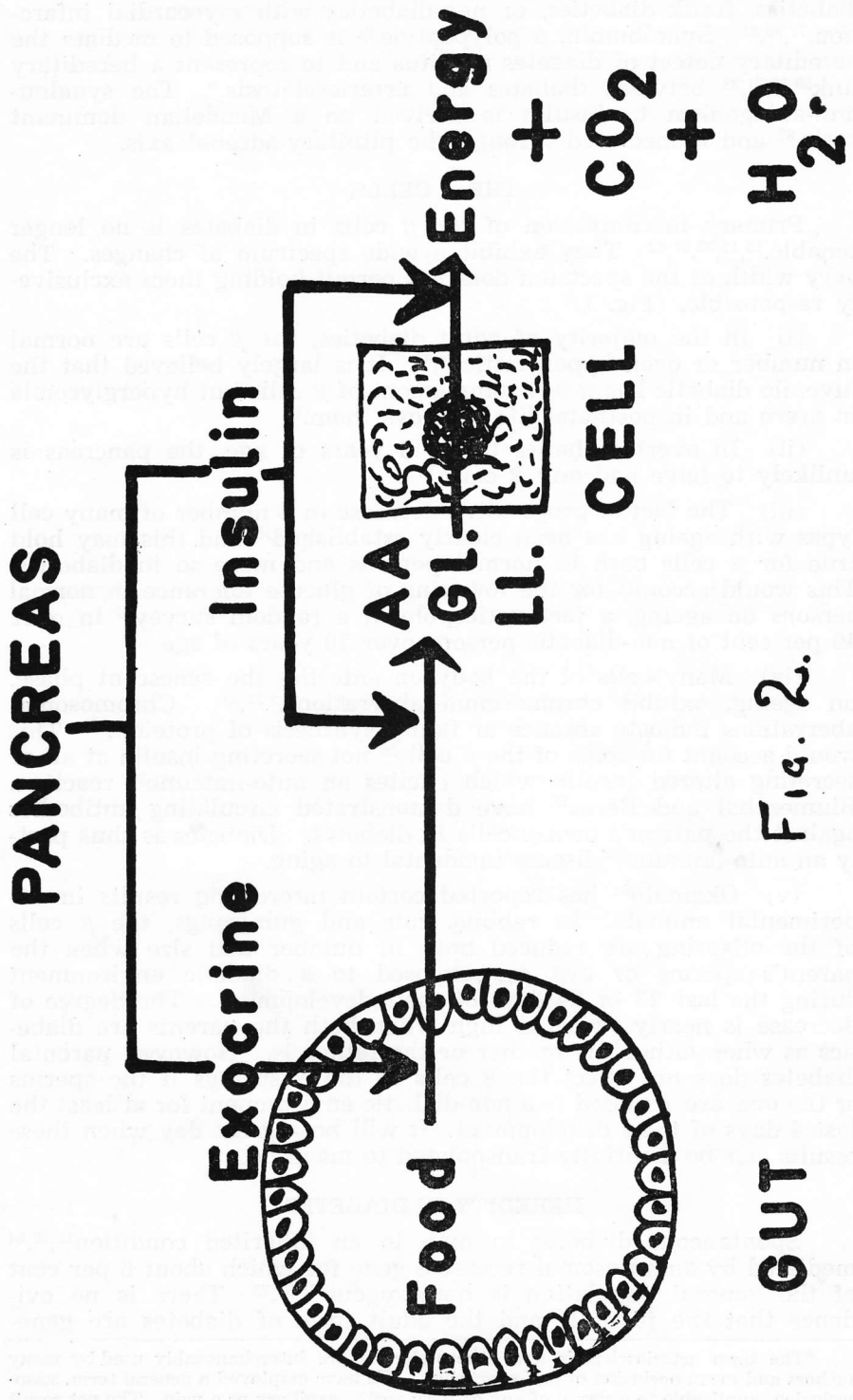
PANCREAS
Insulin
Exocrine
AA
GL.
LL.
Energy
+
$CO_2$
+
$H_2O$
CELL
Food
GUT

FIG. 2.

diabetics, frank diabetics, or non-diabetics with myocardial infarction.[77,80,81] Synalbumin, a polypeptide,[81] is supposed to mediate the hereditary defect of diabetes mellitus and to represent a hereditary link[39,57,81,82] between diabetes and arteriosclerosis.* The synalbumin-antagonism to insulin is derived on a Mendelian dominant basis,[82] and is mediated through the pituitary-adrenal axis.

## THE $\beta$ CELLS

Primary incrimination of the $\beta$ cells in diabetes is no longer tenable.[15,17,39,57,82] They exhibit a wide spectrum of changes. The very width of the spectrum does not permit holding them exclusively responsible. (Fig. 1)

(i) In the majority of adult diabetics, the $\beta$ cells are normal in number or even hyperplastic.[54,82] It is largely believed that the juvenile diabetic has a full complement of $\beta$ cells but hyperglycemia *in utero* and in postnatal life destroys them.[15]

(ii) In overt diabetics under 5 years of age, the pancreas is unlikely to have had any $\beta$ cells.[15]

(iii) The fact of progressive decrease in a number of many cell types with ageing has been clearly established[10] and this may hold true for $\beta$ cells both in normal persons and more so in diabetics. This would account for the lowering of glucose tolerance in normal persons on ageing, a fact noticeable in a random survey[20] in over 40 per cent of non-diabetic persons over 70 years of age.

(iv) Many cells of the body on entering the senescent phase, on ageing, exhibit chromosomal aberrations.[5,24,45] Chromosomal aberrations indicate absence or faulty synthesis of protein.[5,20] This would account for some of the $\beta$ cells[20] not secreting insulin at all or secreting altered insulin which excites an auto-immune[25] reaction. Blumenthal and Berns[16] have demonstrated circulating antibodies against the patient's own $\beta$ cells in diabetes. Diabetes is thus partly an auto-immune[25] disease incidental to aging.

(v) Okamoto[61] has reported certain interesting results in experimental animals. In rabbits, rats and guineapigs, the $\beta$ cells of the offspring are reduced both in number and size when the parent's sperms or ova are exposed to a diabetic environment during the last 23 or 24 days of their development. The degree of decrease is nearly twice as high when both the parents are diabetics as when either the mother or the father is. However, parental diabetes does not affect the $\beta$ cells of the offsprings if the sperms or the ova are exposed to a non-diabetic environment for at least the last 4 days of their development. It will be a great day when these results can be fruitfully transpolated to mankind.

## HEREDITY IN DIABETES

Spontaneous diabetes in man in an inherited condition[15,42,64] mediated by an autosomal recessive gene for which about 6 per cent of the general population is homozygous.[41,57,73] There is no evidence that the juvenile and the adult form of diabetes are gene-

*The term arteriosclerosis and atherosclerosis are interchangeably used by many authors and mean occlusion of major arteries. We have employed a general term, vaso-occlusion, applicable to a vessel of any calibre: aorta, capillary or a vein. The net result no matter what term is used, is the loss of vascular lumen leading to a decline in tissue perfusion and nutrition.

tically distinct.[41] The genetically controlled component may be an insulin-inhibiting factor. The gene may have a variable penetration[41,67] and the overt metabolic disorder may represent the last phase in the development of the disease while premature vaso-occlusion may often precede the metabolic disorder.[41]

The functional role of the diabetic trait in the working of Natural Selection has been discussed by Porter.[64] According to him, at an early stage of evolution when food was scarce, the diabetic genotype may have served as an important energy-conserving mechanism, thus functioning as a thrifty genotype but with the inherent disadvantage, eventually, of overproduction of an insulin antagonist.[59] It is difficult to accept how the genotype could have ever been thrifty, for in the relative absence of insulin the metabolic machinery works wastefully and inefficiently.[15,17,33,41,57]

## OBESITY AND DIABETES

Obesity aggravates, exaggerates or predisposes to diabetes.[42,58,69] At the same time,[57,82] diabetes leads to obesity because of the selectively facilitatory action of insulin on fat deposition[82] in diabetes. Thus diabetes is the cause, and obesity is result.[57,82] It is interesting to note that obesity, in man, is the commonest factor reducing the brain-weight/body-weight ratio, which controls the lifespan of an animal.[70]

## EVOLUTION OF DIABETES MELLITUS

Diabetes is a universal disease of mankind.[42,85] Spontaneous diabetes in the natural state is rare in animals.[11] Its incidence in man is stated to be in the vicinity of 10 per cent of the general population. This would imply that the human diabetic trait has evolved recently in the evolutionary scale.

There are two important natural phenomena that govern the death rate in any animal species. The first is the fixity of the lifespan of each animal species.[22,23,24,45] The second is the phenomenon of Gompertz[35] whereby there is increasing natural mortality with increasing age in each animal species, including the invertebrate, such as Drosophilia melanogaster.[22,23,24,76] This means that the life expectancy in any animal species extends from soon after birth to the total lifespan. The characteristic lifespan of each animal species is genetically determined and this depends upon the programmed aging process which starts soon after birth.[5,22,23,25] Some common aging processes where such genetic progamming is operative in man are coronary atherosclerosis, hypertension, diabetes and cancer.[5]

The Gompertz phenomenon[22,23,25,35,75] in any species is subserved by diseases both intrinsic and extrinsic.[18] In man, medical advances have largely eliminated the extrinsic diseases due to deficiencies or infections.[18] Nature thus depends on intrinsic diseases to bring about increasing mortality with increasing age in man.[45] The two common intrinsic mechanisms (ageing processes, senescent processes, or the so called degenerative diseases) operative in man are[45]:

(i) The intracellular mechanism of cancer and

(ii) The intercellular mechanism of vascular occlusion.

In a society well provided for these two mechanisms account for the majority of deaths at all ages.[5] (Fig. 3) It is submitted that

the diabetic trait assists the second mechanism by expediting its onset as well as progress, so that the latter more effectively subserves the Gompertz phenomenon.

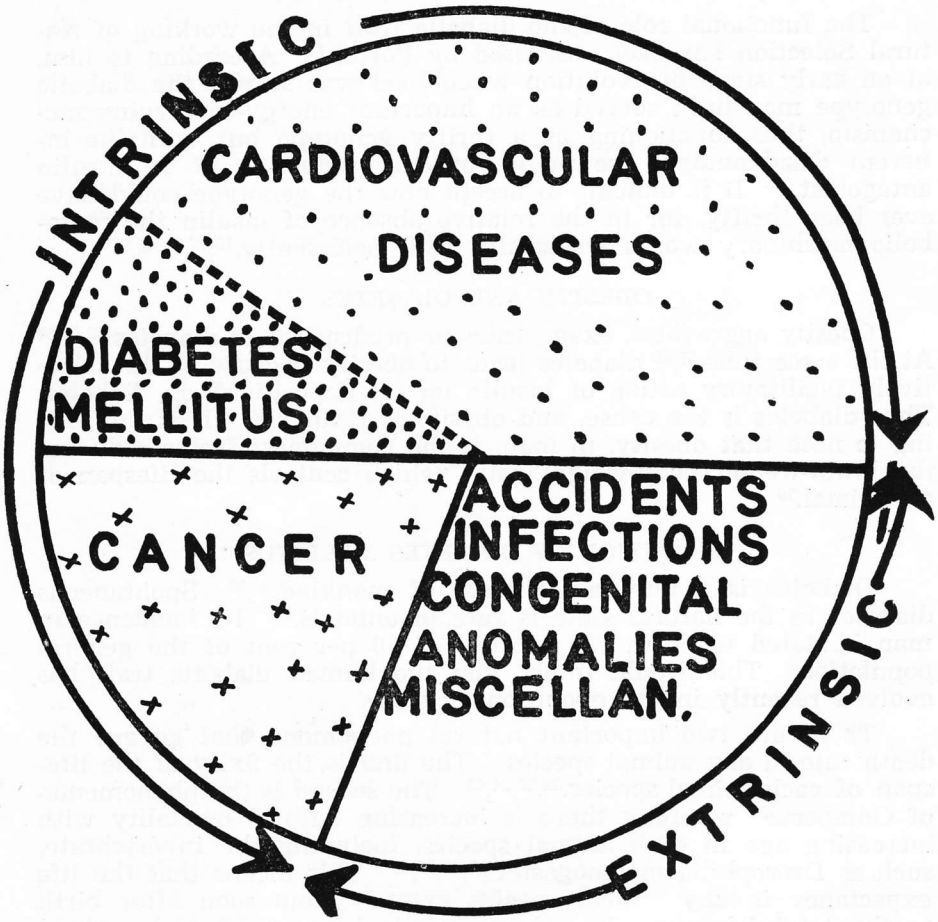


Fig. 3.

As elaborated later, it is not the intensity of diabetes that is important, but it is its mere latent or manifest presence that serves to expedite the vaso-occlusive process.[15,57] In this way, the diabetic trait is comparable to a positive catalyst which expedites a process by its mere presence.[32]

At this stage, the syndrome of diabetes mellitus may well be compared to an iceberg. (Fig. 4) The visible part of the iceberg is the disturbed carbohydrate metabolism, while the submerged part of the iceberg consists of the vaso-occlusive process, widespread in character, rapid in progress and the truly lethal element of the syndrome. Just as a ship is damaged by the submerged part of the iceberg, so is an individual destroyed by the submerged part of the diabetic iceberg. Quite often the damage done by generalised vaso-occlusion is evident before any metabolic abnormality becomes detectable.[30,57,82,83]

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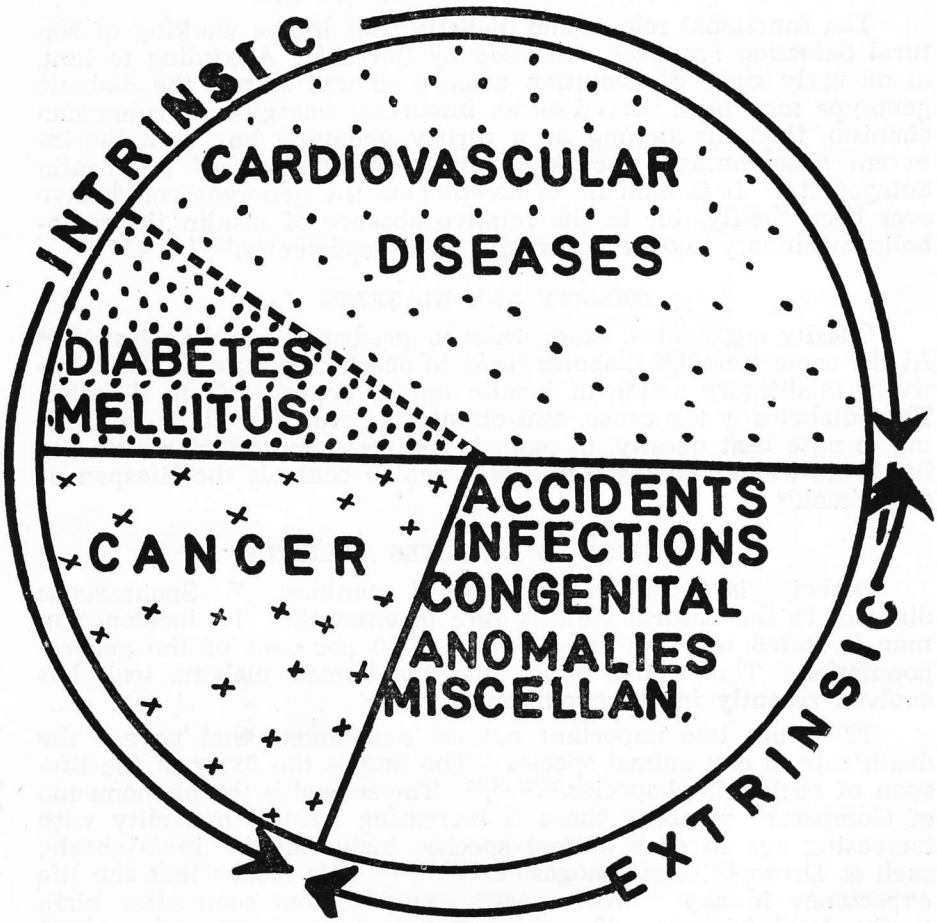


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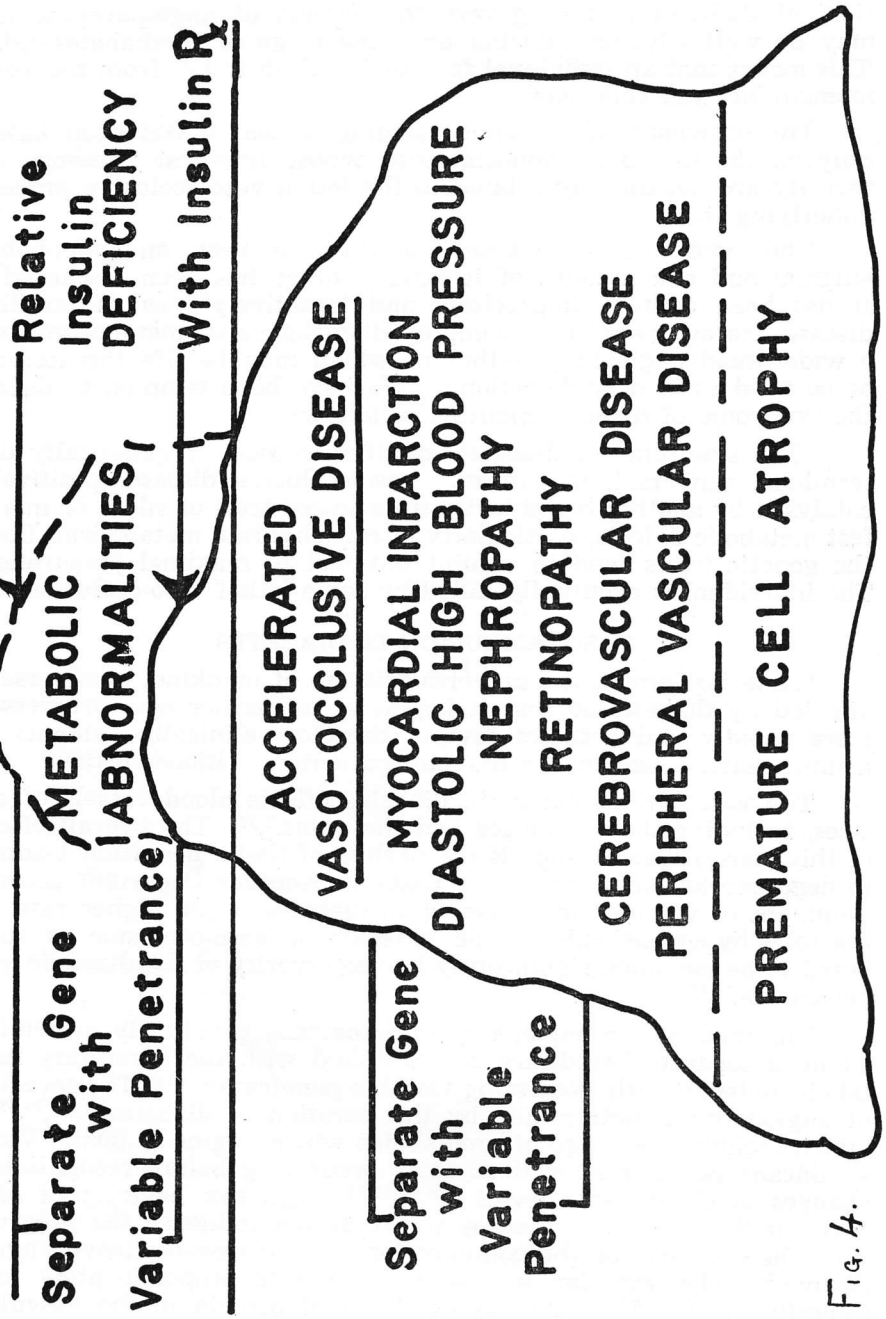


Fig. 4.

Spontaneous diabetes in man has been divided into 4 stages:[15]

Stage 1 : Prediabetes.
Stage 2 : Latent, chemical or subclinical diabetes.
Stage 3 : Chemical or latent diabetes.
Stage 4 : Overt diabetes.

The stage of prediabetes begins at the time of conception of the individual.[57,83] It is supposed to account for the 'total dura-

tion' of diabetes and to govern the process of angiopathy which may be well advanced during even the stage of prediabetes.[14,57,83] This means that an individual is a 'diabetic' *ab initio*, from the very moment he was conceived.

The drawback of the above staging is that it has been based only on the metabolic abnormalities whose manifest presence or severity are not directly related to the lethal vaso-occlusive process underlying it.

The syndrome of diabetes mellitus has been an indefinable enigma[9] and one account of it after another has been discarded.[15] It has been defined, imprecisely and tentatively[57], as "a familial disease characterised by a complex disturbance of metabolism and a widespread angiopathy, either of which may be life threatening or so mild as to defy detection". We have been tempted to define the syndrome of diabetes mellitus as follows:

"The syndrome of diabetes mellitus consists of genetically determined, universal, multiform, vaso-occlusive disease, positively catalysed by another hereditarily transmitted trait of silent or manifest metabolic defects, particularly of carbohydrate metabolism. Both the genetic traits tend to exhibit minimal to maximal penetrance. The individual is eventually killed by some lethal vaso-occlusion/s."

## VASO-OCCLUSION IN DIABETES

"Arteriosclerosis, the universal disease of mankind, is adversely affected by diabetes so that it begins at an earlier age, progresses more rapidly and becomes severe (therefore clinically evident) at a much earlier age in the diabetic patients". (Bloodworth[15])

The vascular involment in diabetes affects blood vessels of all sizes, including the capillaries and the veins.[2,57] The overall effect of this pansystemic change is the decline of tissue perfusion leading to degeneration or death of the tissues. Another important accompaniment of vascular involvement in diabetes is the higher rate of diastolic hypertension.[15,62] The severity of vaso-occlusion is supposed to be mediated significantly by the severity of the diastolic hypertension.[15,62]

The tendency to angiopathy in diabetes is genetically determined by a separate hereditary defect linked with the hereditary metabolic defect,[21] each possessing variable penetration.[56,67] The severity of angiopathy is determined by the duration of diabetes[2,7, 15,39,57,66] which includes the stage of prediabetes which begins at birth. Very significant vascular alterations often occur long before recognisable changes in blood sugar levels.[15,30,39,57,83] Age, sex, severity of diabetes or the efficacy of therapy *per se* do not influence the progression, the severity, or the complications of the vaso-occlusive angiopathy.[7,83] The vascular lesions occur despite proportionately low hyperlipemia.[67] Excessive laying down of protein in the vascular basement membrane due to 'hypertrophy' or 'atrophy' of certain enzyme-systems may underlie some of the vascular lesions of diabetes.[13,34,53,57,72]

The coronary vasculature is the most adversely affected part of the vascular system in diabetes.[7,57,67,83] It is clinically apparent sooner or later in 50 to 75 per cent of all diabetic patients including the juvenile. "Thus, coronary artery disease should be included among the characteristic morphologic commensals or complications

of the diabetic state, together with retinopathy, nephropathy, diabetic neuropathy, necrobiosis lipoidica, etc. Each of these is probably an expression of underlying disease of various elements of the vasculature". (Metz)[57] Cerebral infarction is 2 to 3 times as frequent in diabetics[2,4,7] as in non-diabetics. Peripheral vascular disease is 7 to 156 times more common in diabetes.[2,6,8,34] It must be emphasized that vascular lesions in diabetics structurally do not differ from those in non-diabetics.[15,17,82] 75 to 80 % of diabetics compared to 50 to 55% of non-diabetics die of cardiovascular involvement.[15,31,83]

## DIABETES : A PROCESS OF AGEING AND SENESCENCE

In a higher metazooic organism, as a part and parcel of the total genetic programme,[5,76] deleterious changes (senescence)[49] occur as a function of the passage of time (ageing)[49] from the time of conception so as to constitute self-determined, intrinsic mechanisms which provide on their own for the phenomenon of increasing mortality with increasing age (Gompertz curve)[22,23,25,35,75] as well as terminate the life of an organism at the end of its finite, species-specific lifespan.[19,22,23,24] 'Nature red in tooth and claw'[52] sees to it that, "the same cellular mechanism would prove morphogenetic in the embryo, defensive in the adult and destructive in senescence" (Metchnikoff).[56]

The syndrome of diabetes mellitus in the human is one such senescent mechanism. It has all the attributes [15,17,42,45] (Table 1) necessary for being so qualified. It is progressive, universal,[75] deleterious, irreversible, time-governed, species-specific, genetically determined, involving multiple systems, exhibiting varying degrees of deleterious change (minimum to maximum)[57] and serves a definite purpose in controlling human biomass. It is a disease of the supporting tissue complex*[45] being almost exclusive to man. In the above respects, it bears a very close comparison to the intracellular senescent mechanism of cancer and the intercellular senescent mechanism of spontaneous non-diabetic atherosclerosis, both the latter processes also affecting the supporting tissue complex. Cancer, atherosclerosis and diabetes are intrinsic processes which singly or severally (Fig. 5) obstruct[1] the "supply lines"[47] carrying nutrition to the cells thereby eventually destroying the cells. Just as atherosclerosis[5] and cancer [46] can be temporally advanced by extrinsic influences so also can diabetes be temporally advanced so as to occur at an age earlier than coded in the genetic programme.[57] (Fig. 6) A shorter lifespan of an individual is reflected in the shorter lifetime of the somatic cells of his body.[36,37,45] Premature cataract,[2,40] atrophic gastritis, atrophy of the pericytes and the ganglion cells of the retina[12,15] reflect such a state of affairs in diabetic individuals.

## IMPLICATIONS

The advent of insulin, and later of the oral antidiabetic agents has significantly relieved mankind only[15,31] of the metabolic vaguaries attendant upon diabetes melitus. The deeper angiopathic aspect can only be prevented either by euphanics† or by strictly eugenic marriages.

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*The total Somato-visceral set-up that supports the SNM complex made up of the Sensorium, the Neuronium and the Motorium [27,45]

†A term coined by Nobel Laureate Joshua Lederberg [50] to mean the science of producting better phenotypes by a fundamental alteration of the genotype.

TABLE 1 : *A comparison of cancer, atherosclerosis and diabetes mellitus from perspectives of ageing and senescence.*

| CRITERION | CANCER | ATHEROSCLEROSIS | DIABETES MELLITUS |
|---|---|---|---|
| A. *TEMPORAL* : | | | |
| 1. Commencement | ... The march towards cancer starts after cytodifferentiation by 12th week of I U L. | Streaks of atheroma noticeable at birth. | Known to occur in neonates. Prediabetes, a part of diabetes begins at conception. |
| 2. Phases | ... Latent phase followed by manifest phase. | Latent phase followed by manifest phase. | Latent phase followed by manifest phase. |
| 3. Time governed | ... Manifest phase is a function of time (F C D C). | Manifest phase is a function of time. | Manifest phase is a function of time. |
| 4. Can be temporally advanced | ... By Carcinogens | By diet, obesity, stress | By diet, obesity, stress, pregnancy. |
| 5. Increasing with increasing of age | ... Yes | Yes | Yes |
| B. *GENERAL FEATURES* : | | | |
| 1. Tissue affected | ... Supporting tissue complex; intracellular involvement | Supporting tissue complex; essentially intercellular involvement | Supporting tissue complex; essentially intercellular involvement. |
| 2. Intrinsic | ... Yes; part of biologic trajectory or genetic programming. | Yes; part of biologic trajectory or genetic programming. | Yes; part of biologic trajectory or genetic programming. |
| 3. Involvement of multiple systems | ... Primarily involves one system; metastases involve multiple systems. | Generalised process; death usually due to lethal occlusion in one particular region. | Generalised process; metabolic disturbances in addition. |
| 4. Degree of change | ... Minimum to maximum | Minimum to maximum | Minimum to maximum; metabolic abnormality and angiopathy exhibit minimum to maximum changes independent of each other. |
| 5. Ontogenic effect | ... Blockage of supply or exit lines; toxaemia of cancer; eventual loss of cellular nutrition. | Blockage of 'life line' to cell with loss of nutrition | Blockage of 'life line', with disturbed enzymatic machinery. |

TABLE : *A comparison of cancer, atheroselerosis and diabetes mellitus from perspecitives of ageing and senescence. (Continued)*

| CRITERION | CANCER | ATHEROSCLEROSIS | DIABETES MELLITUS |
|---|---|---|---|
| 6. Species-specificity ... | Yes ; highest incidence in man. | Yes ; highest incidence in man | Exclusive to man. |
| 7. Biological significance... | Inexorable expression of cell's ability to 'destroy'; part of 'Nature red in tooth and claw.' | Inexorable expression of cell's ability to, 'destroy'; part of 'Nature red in tooth and claw'. | Inexorable expression of cell's ability to 'destroy'; part of 'Nature red in tooth and claw'. |
| C. *HEREDOFAMILIAL ASPECTS* : | | | |
| 1. Type ... | Many cancers are now shown as familial; clear evidence of hereditary transmission in only 4-6 type of cancers | Heredofamilial | Heredofamilial |
| 2. Nature of inheritance... | Multifactorial inheritance Autosomal recessive gene for clearly inherited cancers. Presence of facultative cancer genome prerequisite in tissue affected. | Multifactorial inheritance | Recessive gene; concurrent gene mediating angiopathy. 6% of the population homozygous for these genes. |
| D. *CRITERIA LAID DOWN BY STREHLER* : | | | |
| 1. Universal ... | Universal disease of mankind; universal distribution in the animal and plant kingdom. | Universal disease of mankind; can be induced in animals; spontaneous incidence in animal negligible. | Universal but exclusive disease of mankind; can be induced in animals. |
| 2. Progressive ... | Yes | Yes | Yes |
| 3. Deleterious ... | Yes | Yes | Yes |
| 4. Irreversible ... | Yes | Yes | Yes |

Compiled on the basis of data available from various sources. (15, 18, 22, 23, 44, 45, 46, 47, 49, 57, 75).

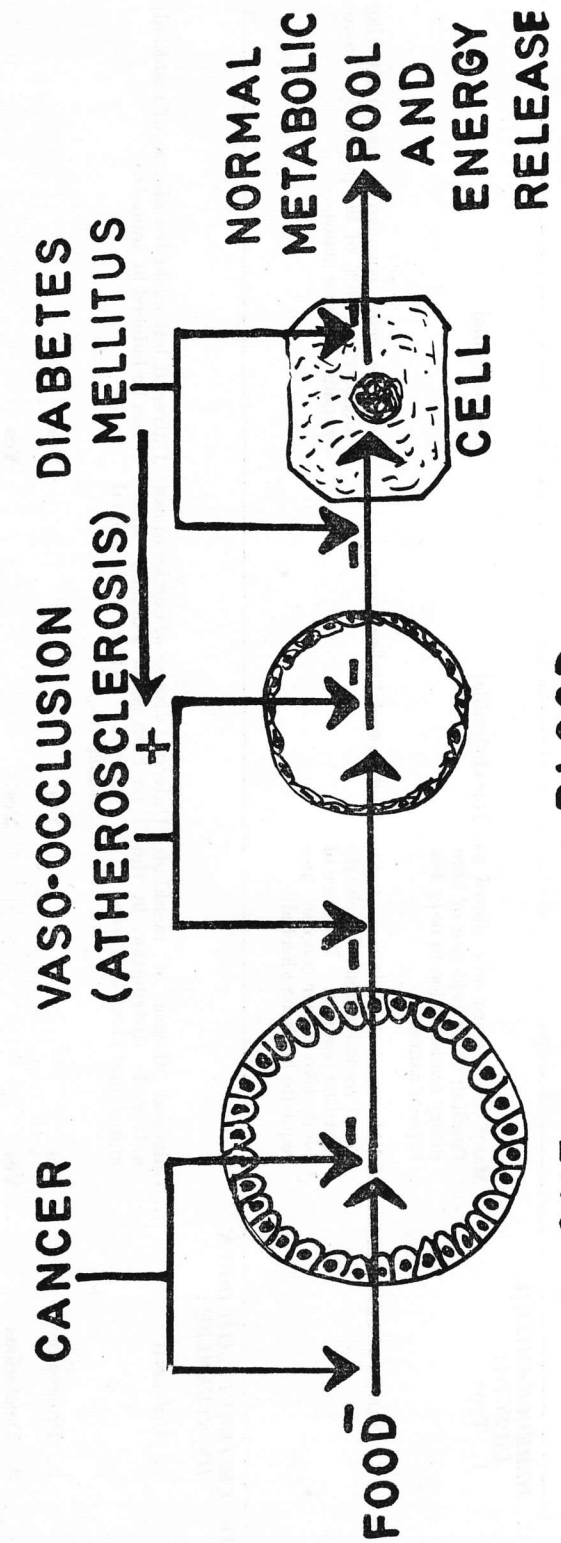
CANCER
VASO-OCCLUSION
(ATHEROSCLEROSIS)
DIABETES
MELLITUS
NORMAL
METABOLIC
POOL
AND
ENERGY
RELEASE
CELL
BLOOD
VESSEL
GUT
FOOD
+
-
-
-
-

Fig. 5.

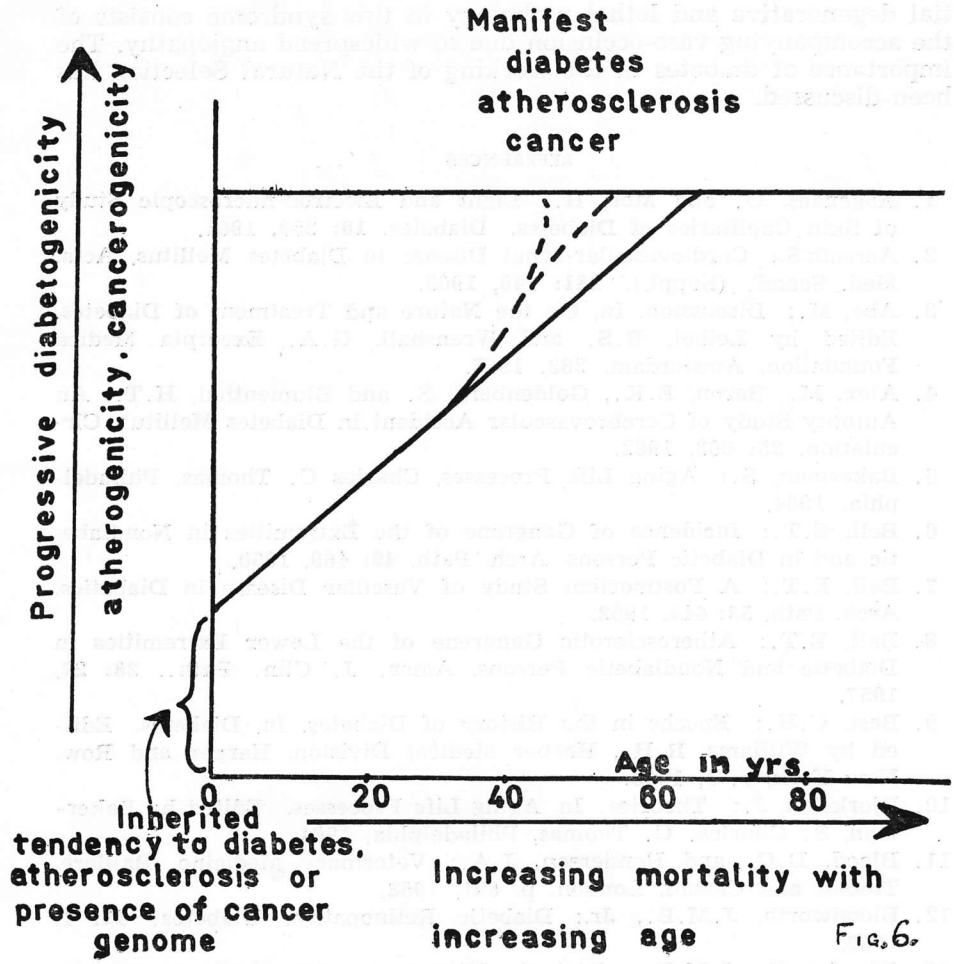


Fig. 6.

All the medical advances put together have not increased the lifespan of man nor have they altered the natural course of the intrinsic senescent processes, which have been considered a normal part of an individual's development.[23] This tantamounts to unkindly stating that the syndrome of diabetes mellitus is a genetic gift to the individual that will inexorably take his toll at the appointed time or even earlier.[57] After over a 100 years of research in cancer one thing we know about it is that we know nothing about it[38]. So in diabetes, the words of William Boyd,[17] at the beginning of the article, leave us rather chastised. The same is applicable to atherosclerosis as well.

The undercurrent of lethal angiopathy in diabetes is like the unvisited, unexplored dark side of the moon. Our hope against this inexorable aspect will lie in unearthing a metabolic or genetic defect that is squarely responsible for this, and in taking appropriate measures against it.

SUMMARY

The evolution and the nature of the syndrome of diabetes mellitus in man have been presented. It has been shown that the essen-

tial degenerative and lethal pathology in this syndrome consists of the accompanying vaso-occlusion due to widespread angiopathy. The importance of diabetes in the working of the Natural Selection has been discussed.

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Original Article

# The Nature of Immunity - Part I

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**Abstract**

An unorthodox approach to the nature of immunity is presented, differentiating it from reactivity. Immunity is a gestalt force, all to the good of an individual, making the concept of autoimmunity ridiculous and rejectable. Reactivity is a vector force that may protect or persecute; it is basically concerned with restoring the integrity of the human body. The concept of cytologue amplifies the idea of integrity, and allows reactivity to fight a microbe, heal a wound, reject a graft, and give rise to "autoimmune" disorders, by means of a concerted CelluloHumoroVascular Response.

## Immunity: Friend or Foe?

As of 1976, medicine knows not what immunity stands for. We extoll its virtues by pontificating that "Man lives in a sea of microorganisms; the immune system is his license to survive."$^{\alpha}$ (Good),[22] an eulogy that turns counterfeit when Burnet[8] declares that immune mechanisms are "more basically concerned with the control of tissue integrity and reaction against recognised anomaly in tissues than in defence against micro-organisms and the production of antibody." This Burnetian concept of "immunologic surveillance"[9] loses credibility on Burnet postulating that it is the immunocyte itself that breeds all autoimmune diseases and on Walford[54] generalizing that all degenerative processes are attributable to immunity. The final *coup de grace* comes from Prehn[45] when he ascribes cancerogenesis to immunity.

## Our Ignorance is our Forte

Our ignorance of the *raison d'etre of* immunity is our forte: we can twist and turn immunity the way it suits medicine's whims and whams. "Immune Responses Can be Variously Manipulated For Patients' Benefit." Under the aforestated heading printed in bold, Lele[40] very recently promised: "Our clinical goals are therefore divergent.... Whereas the goal in infectious diseases is to enhance the immune response, the goal in organ transplant is to induce immune tolerance. The goal in cancer therapy is one of terminating unresponsiveness to the tumour antigen, while that in autoimmune disorders is one of re-establishing unresponsiveness to 'self' antigens." Immunity seems to be every medical man's fool.

## A Wasteland of Words

A major side effect of the above comedy is that immunology, as a science, is a semantic jungle, a wasteland of words, "encumbered by a wretched and baffling vocabulary unmatched by any other science."[21] The outcome is predictable: "Immunologists speak only to immunologists, and even then it is open to question whether one immunologist knows what another immunologist is talking about."[21] The fundamental words *antigen* and *antibody* are inept and confusing, and immunity still goes abegging for a definition, what to talk of the semantic atrocity *autoimmunity* which is supposed to connote immunity turning against the host. The rank antibody-ism of immunologists is their *exaggerated sense of humour* that is not only confounding but can be quite boring.

## A Non-Anthropocentric Approach

The essence of *immunity* is shrouded in anthropocentrically used "military"[20] *terminology - defense, offense, destruction* and the like. By all dictionary and textbook definitions, immunity is supposed to be defensive; yet when it lets loose some antibody into the circulation as in rheumatoid disease, it is incriminated as self-destructive or autoclastic.[5] According to what suits them, immunologists declare immunity as *defensive* when some antibody against a cancer is detected, and as *destructive* when lymphocytes are found focally in

various "autoimmune" diseases, hence justifying the whipping up of immunity in cancer and the smothering of it in "autoimmune" disorders.

The situation is rendered much clearer, however, if we eschew the *defence-destruction-business* and look upon immunity as a vector force that turns out to be *good, bad* or *indifferent* depending on its strength, direction, and the target it works at. It is a homeostatic/histeostatic mechanism that like any other mechanism e.g., vasoconstriction or catecholamine release in shock could work as much for as against the organism.

## A Plea for Pluralism

In the current era of immunology, immunity/immunology is supposed to be represented only by the trio of *antigen, antibody* (cellular or humoral), and *antigen-antibody-reaction.* But there is far more than meets the immunologist's eye - macrophage, neutrophil, platelets, eosinophils, clotting mechanism, the fibroblasts, the serous membranes and what not.[19,63,64,65] One and all of these work alone or in concert, with antibody or the lymphocyte if need be, to strive at or ensure histeostasis. A sentence from Kurt Vonnegut[52] is to the point: "My adrenal gland gave me a shot of adrenaline.... It also caused coagulants to pour into my blood stream, so in case I was wounded, my vital juices wouldn't drain away." Intact epithelium over a fractured bone is far greater an immune force than all the antibodies and immunocytes put together. Remove the epithelium, and the *open* fracture turns infected, osteomyelytic and prone to delayed union.[1] Blood vessels are indispensable to any immune process-reactive, reparative, or rejective. A wound would not heal unless the blood vessels initialy obliged by proliferating, later by perishing, and the epithelial cells did not reactively multiply to bridge the gap. Immunity, thus, is a concerted effort of *cells, humors, and blood, vessels,* which, by mostly *reacting* to a situation of disturbed histeostasis, comprise CelluloHumoroVascular Reactive System (CHVRS). On a closer scrutiny, one would realise that *the greater* truth is *not immunity but* reactivity - reactivity that saves when operative against a wound or Salmonella typhi, but which kills when

berserk against a few molecules of benzylpenicillin, or a CNS that has the temerity to share some antigens with a tiny bronchial carcinoma.

## Cytologue: A Concept

The human body is an assemblage of 6000 billion cells-2000 times more in number than the present world population, each cell as complete a representative of life as the host individual. (The blue whale weighing 150 tons comprises about 12,000,000 billion cells). These myriad cells hang on to each other without rivets and screws, multiply, migrate, fall off, secrete, and do so many other things that leave us wonderstruck. Each cell carries around itself an *individuality,* a uniqueness that is *unprecedented, unparalleled.,* and *unrepeatable* and which is representative of the uniqueness of the host. Lewis Thomas[51] succinctly descri-bes this cellular/human uniqueness: "Everyone is one in 3 billion (the total human population today) at the moment.... Each of us is a self-contained, free standing individual, labelled by specific protein configuration at the surface of cells.... to the extent that a fragment of cell membrane will be recognised and rejected between any conceivable pairs among the 3 billion, excepting identical twins." In a person, then, each cell is an untamable I-specialist, that will only tolerate another cell with which it can see I-to-I.

All the cellular stars in a cytogalaxy called an organism *stay put* in cohesion and work in unison by conversing with one another through an organism-specific code of communication; they recognise *friend-or-foe* by using such a code as a password. This "call of cell to cell" - called *cytoclesis* by Wood Jones[57] - in an individual is what can be called *cytologue.* An immediate corollary of such a concept is that any breach or interference in this cytologue would be recognised as threatening the organism's *integrity,* and the organism, in turn, would *react* to set things right and see that the head-to-foot *gestalt* cytologue is reestablished.

The breach in cytologuic wholeness may occur through *discontinuity* as after injury or infarction, whereas interference may be sensed following (i) *deselfing* of self-cells (suicytes)

and/or self-elements (sui-elements') leading to the so-called auto-immune phenomena, (ii) the presence of *foreign cells* as after an allograft, (iii) the presence of *microbes,* and (iv) the presence of *a foreign body* like the one that Elie Metchnikoff put into the starfish larvae in the Straits of Messina in 1882, a simple experiment that was crowned by a Nobel prize in 1908. The foregoing cytologuic concept accounts for the hitherto ill-understood fact that our body treats injury, infarction, infection, allografting, or foreign body by a prototype cytohumorovascular response generally called *inflammation* and eulogized by Howard Florey[19] as "the backbone of pathology."

## Evolution of CHVRS

Heterotrophism is another way of saying that *life assimilates life,* through the digestive lining, a biophenomenon that may have determined the entodermal lining as the prime source of the cells of the "immune" system to oversee that nothing that comes patently as not-self (called "food") manages to get into the organism in the not-self form, nor survive as such within the organism. It is little wonder, then that the bursa of Fabricius (antibody production) and thymus (immunocyte production), the key organs governing "immunity", develop from the entodermal lining.[27] The equivalent of the bursa of Fabricius in man is GALT - Gut Associated Lymphoid Tissue.[30] The ubiquitous macrophage/phagocyte originally lined the digestive tract of the coelenterates[18] and served as the foodpicker for the hydra. That very phagocyte, in man, has not lost its digestive enzymes which can take care of the phagocytosed microbe. Animal life's decision to assimilate life and to sustain upon it without disturbing its own cytologue forced upon it the evolution of the very complex "immune" system off its primitive looking entodermal lining. Let us say a "Hurrah" for Nature's foresight and versatility. Lest it be forgotten, the "immune" system starts operating right at the level of the starfish larva, or the earthworm.

## CHVRS and Histeostasis

The CelluloHumoroVascular Reactivity, usually called immunity/immune response, is designed to *recognise*

cytologuic disturbance, react against the injured/altered (self) or intruding (foreign) elements, *remove/reject* them, and finally to *restore* the involved tissue or organ to as near status quo ante as possible. Such a mechanism can be designated *histeostatic* comparable to the *homeostatic* mechanism, conceived and popularized by Walter Cannon.

We may understand how the new concept outlined above differs from the traditional idea of immunity. Halpern,[26] writing on the subject in *Allergy* '74, presents this traditionality: "The survival of highly developed organisms is dependent on the absolute integrity of `self', in other words the unfailing recognition animate or inanimate aggressors. Only a system capable of detecting the most subtle of molecular differences is in a position to ensure the efficient protection of the organism." Halpern's definition is militaristic; it talks of the need to detect "the most subtle of molecular differences" without telling why should this be such a compelling imperative; further it alludes to "protection" of "the absolute integrity of `self' " without explaining how a minor scratch while shaving, in no way "endangering" the life of the organism, excites the same tissue response as does an infection or a major trauma;[4] lastly, and most importantly, it is unable to explain the not uncommon paradox of this protector turning into a persecutor, or of the immune system treating its own injured/infarcted tissues_ with the same relentlessness as it treats a foreign body or a graft. The concept of cytologue-and the cytologuic imperative to remain undisturbed makes it comprehensible that the "aggressors" can arise as much from within as from without.

Immunity/reactivity may be, for an organism *good, bad, indifferent,* or a mixup of these. That most human beings are able to merrily live out their total lifespan means that the wages of immunity/activity are largely good; the fact that the picture in Goodpasture's syndrome, or SLE, is quite devastating implies that the wages can be bad; the occurrence[54] of increasing levels of "autoantibodies" (more truly, antiautobodies) with increasing age, without our being able to really incriminate them for pathogenesis, is an example of its indifferent nature. It is interesting to see what makes

for this goodness, badness and indifferentness, with the important proviso that immunity and reactivity be treated as separate from now, immunity enjoying its pristine connotation of all *good for an individual,* and *reactivity* meaning a force good, bad or indifferent.

## Hail Immunity

Epistemologic, etymologic and eusemantic considerations compel the assertion that *immunity* ought to mean unalloyed *good* for an individual. Immunity *(L. immunitas;* Fr. *immunis)* implies "freedom or exemption from a charge, duty, obligation, tax, imposition, penalty, or service"[55] and connotes aristocracy on the part of an organism whereby it does not have to enter into *a reactive quarrel* with things from without or within. In its real sense, then, *immunity is nonreactivity.* Whenever CelluloHumoro. Vascular System comes into operation, it becomes *reactivity* which may be good, bad, or indifferent. Immunity and reactivity are poles apart and should be treated as such. Geneticists, anthropologists, phylologists, endocrinologists and many others who have nothing to do with a bacterium or virus *versus* the human body and yet are claiming to be working on immunochemistry, immuno-assay and the like, had better accepted that they are exploiting the "reactive" faculty of the human body, thus working truly on reactive-chemistry for immunochemistry, genetics of reactivity for immunogenetics, radioreactivity-assay for radioimmunoassay, and the like.

## Nature of Immunity

Immunity, mediated *by immunity g mechanisms,* strives at keeping an organism's cytologue in a *gestalt* state by preventing the intrusion, into the organism, by members of the microbial ocean that a metazoic organism swims through, during life. The immunity mechanisms comprise a variety of forces, the prime one being the intact epithelial sheet that covers the cutaneous and mucosal areas of the body - all areas that come or could come in contact with the *milieu exterieur.* This provides, for the organism, a virtually impervious envelope, a close mimicry of which is to be found in serous cavities.

The impervious cytosheet covering all the mesothelial cytosheets lining the the exposed areas[3] of the body is protected by a number of *surface-forces*- physical, chemical, humoral, cellular, and, *it may appear strange, microbial.*

The physical group comprises: (a) the ceaseless exfoliation of all epithelial cells - cutaneous and mucosal, whereby microbes are, as it were, pushed away from the body; (b) the continuous flow of fluids from the secreting surfaces, through the ducts, to the exterior; (c) pH differences: "The skin usually has an acid pH and this tends to inhibit the growth of most disease-producing bacteria..."[60], such low pH is present in the stomach and in the vagina; (d) the ciliation in the respiratory tract that keeps the lower respiratory tract virtually sterile.[37]

The chemicals are the ubiquitous lysozyme and such bactericidal substances as the long chain fatty acids in the secretions of the sebaceous glands. The important surface humour is IgA.[48,60] Phagocytes-as over the lung alveoli's[48,61] - constitute cellular moppers for the microbes. Each epithelial surface has its own indigenous microbial flora[60] - microbiota - which through metabolic competition and production of germicides such as organic acids prevent infection.

*Premunition,* called the phenomenon of *infection immunity*[15] - *is* an example of a thief guarding against a fellowthief, a compelling evidence of the beneficial effects of macromicrobial coexistence. "It has long been recognised that the persistence in the body of a given microbial agent is accompanied by a high level of resistance to superinfection. Such a state of resistance was early recognized and designated as infection immunity or premunition. Although emphasized chiefly for its relevance to malaria, tuberculosis, syphilis and relapsing fever, infection immunity is certainly of very general occurrence, but its study has been grossly neglected."[15]

"One of the remarkable facts about immune mechanisms is that anitbodies (or anticells) are not formed against the body's own tissues; that is, the antibody forming mechanism can

differentiate between `self' and `not-self'. A state of tolerance towards a potential antigen (from within) is acquired during pre-natal and early postnatal life."[29] The *state of tolerance* is a facet of immunity whereby an individual *does not react to* his own tissues and elements, and is achieved during prenatal, and early post-natal life through a process of "immunologic maturation"[29] whereby cells capable of reacting against the body's own cells/elements are eliminated. Acronymically, this could be called CARE-. ContraAuto Reactivity Eliminated, Burnet and Medawar got their Nobel prize for showing that if foreign cells are introduced into an organism prior to CARE, the guest cells are accorded self-status (they are *`self ed') by* the body through elimination of reactocytes capable of reacting against the guest antigens. This freak - found in natural/artificial chimera can compel CARE to be rarely read as Contra Allo Reactivity Eliminated. It is interesting that the CARE process works only for cells that are actively dividing (possibly presenting thereby their antigens, to the reactocytes) so that cell-systems that stop dividing very early in development (sensory cells, neurones, muscle cells) are not CAREd or selfed, making them constitute, for the organism, "occult" antigens (literally meaning hidden not-self elements). Throughout life, cell-systems possessing occult antigens are guarded against "immuneinvasion" by a protective barrier, possibly akin to the epithelial barrier found in the thymus.

The Orwellian double-speak of immunology has fostered the present view of a Janus-faced immunity, as bad as it could be good - *immunitis divinitas et devilitas.* A burden of this article is to divest immunity of this conceptual and semantic diabolism and restore to it its pristine meaning of *good, whenever operative.* Immunity becomes, then, incapable of doing any harm - a conceptual clarity that does away with such semantic atrocity as *auto-immunity* and which takes away from the realm of immunity such tissuesores as allergy and hypersensitivity, relegating them to the arena of *reactivity.* It *is immunitas divinitas,* the *devilitas* role being taken by reactivity depending on circumstances.

In the above elaboration of the nature of immunity, no reference has been made to the role of immunity in fighting/

preventing autochthonous cancer. Such a view is a direct antithesis of today's raging fashion that *immunity* protects against cancer. "From the human and medical angles... without immunological surveillance, cancer would be more frequent and occur at younger age than it does."[9] Elsewhere,[8] in support of immunological surveillance, Burnet fantasizes a situation where cancer cells from an adult could implant into an abrasion on the skin of an infant, adding that "to prevent such a calamity we believe that nature, to speak teleologically, invented the mechanism of vertebrate immunity." Yet, regardless of the immune surveillance, cancer afflicts humankind unimpeded, forcing Burnet[9] to recant and declare that the outcome of cancer research including the immunological approach, has been "precisely nil" and that "Nothing of value for either prevention or cure has come from the laboratories."

Both "tumor immunity" and "transplantation immunity" are laboratorial artifacts that have little to do with biologic reality. Oceanic research on the former has proved its worthlessness; the latter is rich with the unending promise of the soon-to-dawn transplant era. A doctor-patient's personal experience[11] with such adventurism at the renal level is reminiscent of the Spanish Inquisition. Transplant era will not dawn for it has no backing of a preceding night, anywhere near reality.

The only area where the "immunologic surveillance" operates is in attacking and eliminating an individual's deselfed suicytes/sui-elements, but there the surveillance is not immunologic but reactologic as rendered clear by what follows.

## The Nature of Reactivity

The etymologic bulldozer capable of demolishing the immunologic Tower of Babel is the word *reactivity.* It stems from the root *react* meaning[47] "to act in return on an agent or influence," or "act reciprocally upon each other," or "to act in opposition, as against some force." The foregoing are pregnant with the *anti-* (= against) emphasis in the two fundamental but ill-conceived immunologic terms *antigen* and *antibody.* Let *antigen* be replaced by the term *actant,* and

conceptual/semantic clarity starts. An *actant* acts to which an organism/tissue reacts; the faculty to react is reactivity; the process is reaction mediated by reactocytes and/or reactins (humours/antibodies), the science is reactology. There is no antigen-antibody reaction but actant-reactant interaction. In such refined context, immunoassay becomes reactoassay, immunochemistry becomes reactochemistry and so on. Reactivity is both non-specific (wound healing) and specific (Rh-reactivization of a negative mother by her Rh-positive fetus).

Specific humoral reactivity - that wondrous faculty of the vertebrate organism to throw *a reactinic tat (antibody) for an actant tit (antigen),* with nearly unparalleled lock-and-key specificity - has been the be-all and end-all of "immunology" modern and ancient. This very obsession has been immunology's undoing, for it has blindfolded until today the researchers to the facts that (a) such specificity has so often very little to do with an organism's immunity, (b) that an antibody has been proved time and again to be antihost, and (c) that the *eureka eureka* trumpeted by cancer immunologists on the finding of an *anticancer antibody* has ended with the realisation that such antibodies in fact protect the cancer against the host's immune system by subversively coating it.

The service rendered by immunology's antibody-ism hinges on the lock-and-key specificity involved. It has helped study of phylogeny by being able to tell, that a baboon is closer to man than a bat. It has facilitated medico-legal investigations, hormonal estimations to the levels of a nanogram, and offered evidence of the interaction an organism has had with an actant (e.g., Widal test). The therapeutic help has been limited. "Passive immunization" has proved hazardous (ATS therapy), save for such areas as snakebite or gas-gangrene. Probably the greatest therapeutic impact of the knowledge of specific actant-reactin interaction, and its avoidance, has been in making blood transfusion a safe affair.

Original Article

# The Nature of Immunity - Part II

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## Towards a Definition of Reactivity

A science lacks direction when it lacks definition. (Incidentally, such a commonplace thing as diabetes mellitus[35] or essential hypertension[44] has remained undefined). Reactivity, therefore, must be defined, being open to definitional refinements with evolution of greater comprehension.

There are some terms to be understood before we go to the definition proper. Self/not-self idea makes no sense when one realizes that (a) a patently foreign cell-system can become part of one's self thanks to the natural or artificial chimerism, (b) one's own cells - "me own flesh and blood" - can too often prove foreign, to breed what is called autoimmunity, (c) one's neurones and muscles immunologically may prove more *foreign* than many a microbe.

There are, then, no self cells, but a *selfing* process that occurs, in man for example, during the later half of intra-uterine existence and early part, of post-natal life whereby the body decides what it is going to treat as its own. The human embryo, constituting a more-or-less completely formed human individual by about the 10th week of gestation,[3,27] is made up of *suicytes* - *its* own cells. The process of "immunologic maturation," CARE, or selfing allows the suicytes to be classified into selfed/CAREd suicytes and unselfed/unCAREd suicytes (neurones, for example). In a chimera, the guest cells are accepted as self, by being selfed. The guest cells, thus constitute, *selfed* allocytes. Anything else - cells, cell

products, inanimate material - not belonging to the selfed category (suicytes/allocytes) constitutes not-self, Suicytes/ sui-elements that, through injury, mutation, degeneration[α] or any other process like binding to a drug or microbial elements, cease to confirm to the selfed-pattern become deselfed, and turn into actants or "autoantigens." (The reactocytic hell that a body lets loose on a kidney in SLE is because of the *deselfing* that the renal tissue undergoes from time to time. Deselfing is the basis of "autoimmunity"). While at terms, the good, bad, and indifferent aspects of reactivity can be acronymically expressed as PAR, CAR, and KAR. PAR is ProAuto Reactivity, CAR is ContraAuto Reactivity, and KAR is a hybrid term to be read as *Koremonai Aremonai* Reactivity. Needless to elaborate, CARD stands for ContraAuto Reactivity Disease, hitherto called autoimmune disease. Severe anaphylactic reaction is an extreme example of CARD, while allergy or hypersensitivity represents it in milder form.

Any reactive process is made up of PAR, CAR and KAR in varying proportions: tuberculous meningitis, for example, is successfully combated by PAR, but it leaves behind a trail of paralyzed nerves engulfed in the fibrous tissue generated by the antitubercle PAR. May be, that is the reason why *immunity* stands for no *reactive* quarrel, as far as possible. As a wag put it, `in a war it is not impor-tant who is right, but who is left.' The body follows this lesson by insisting that immunity is absence/avoidance of reactivity.

The above principle found its immediate and profound impact in the *Listerian et Semmelweissian* principles of asepsis and antisepsis which are, apart from immunity, the means of avoiding a confrontation or a reactive showdown with the microbes - a kind of Swiss neutrality, a refusal to enter into a potentially dangerous dialogue. The gains have been the *tour de force* of modern medicine: "Actually. in terms of lives saved, the development of sanitary measures such as antisepsis and sanitary control of food, water, and insect vectors, represents the greatest single lifesaving achievement in medical history."[56]

Reactivity may now be defined as cellulohumorovascular activity comprising focal, local and systemic formation and

presence of extraneous specific and non-specific cells and humours that aim penultimately at restoration of the body's integrity to as near to status quo ante possible, the reactivity response having been excited by disturbances in the cytologue due to the presence of (i) damaged, dead or deselfed suicytes/sui-elements, (ii) any inanimate material (iii) microbes, or (iv) allocytes/allo-elements, the entire process passing through the phases of recognition, reaction, removal of the disturbing cells/elements, and restitution to status quo ante with the help of such processes as replication of missing cells (e.g., epithelial cells, liver cells), vascularization, devascularization, and contracture of the matriceal fibrous tissue. Nature's masterstroke vis-a-vis reactivity was to ask the ubiquitous fibroblast to provide the fibrous scaffold for any reac-tive focus, so that the inherent contractibility of the fibrous tissue would help eventually to reduce the focus to the smallest possible size, on completion of the job.

## Reactocytes/Reactocompetence

Halliday,[25] the author of "Glossary of Immunological terms" defines immunocytes as "Cells concerned in immunity, *especially antibody-formation".* The latter italicized part of the definition betrays the all too common antibody-ism. When it comes to defining immunocompetence, the antibody-obsession is no less: "Immunocompetent cell: Any cell which can be stimulated by antigen to either form antibodies or give rise to cells which form antibodies".[56] If the oversung antibody has proved such a grand illusion as far as immunity goes, why not extend the honour of immunocompetence to a macrophage or to an epithelial cell which, with palpable competence, provide positive protection to an individual. Any cell, then, that partakes in offering immunity is an immunocyte/immunocompetent cell. The "immunocyte" in the definitions stated above can be reactocytically understood by being designated *specific. A* specific reactocyte is one which secretes a specific reactin against an actant or can combine directly and specifically with that actant. When such a process occurs *in vivo,* the background but vital performance is by the unsung macrophages, complements, reticuloendothelial cells, and so on each of which is a reactologically competent in its own right.

## PAR, CAR and Vaccination

Vaccination, often called active immunisation, illustrates very well the fundamental differences between *immunity* and *reactivity.* Firstly, it is wrong to call such a procedure as immunisation for what is gained is not immunity but reactivity which may be absent, adequate, injurious or fatal. (The fallacy is much greater when injection of ATS or any other serum is called passive immunisation, which could be but a way of killing a person). Small pox vaccination presents a case in point. It may not take. So often, it succeeds in arming the individual with adequate reactivity against the virus. It may prove a nuisance, since the reaction of the body to the vaccine may lead to "progressive necrosis of the skin at the vaccination site and the development of metastatic lesions in other areas of the skin and in the viscera".[48] Sometimes, it may lead to "postvaccinial perivenous encephalitis" which is nothing but fatal.[53] It should thus become clear that vaccination - no longer to be turned immunisation - is blessed with PAR, fraught with CAR and is basically a process of eliciting in the individual what may be called *thwartive reactivity,* outlined below.

## Thwartive Reactivity

*Thwartive* (from thwart - "to oppose successfully; to prevent from. accomplishing a purpose"[47]) *reactivity* (also called *thwartivity) is* the ability of an individual to knock a microbe, an allocyte or an allo-element out of action by means of cells and/or humours, specific and/or non-specific on the latter entering the individual's body past the immunity barrier, this being an active arrestive response by the organism against the intruding element with which it came in contact earlier, accidentally or by design.

The evolution of thwartivity is important both ontogenically and phylogenically - as a phenomenon evolving both horizontally (in a herd) and vertically (through generations). For example, infection with tubercle bacilli, *for the* first time, in an individual or a group excites a reaction that may be mild, moderate or severe, silent or symptomatic. This can be called the initial reaction which serves to (a) fight against the intruder, but more importantly, (b) to prime the organism/

s to react thwartively - thwartive *reaction* - against subsequent infections by the mycobacteria. At phylogenic level, the evolution is slightly different. A generation gets infected by tubercle only to succumb to it. The lethal brush with the microbe however does not go wasted, for the subsequent generations grow more and more resistant to the bacillus, by exhibiting strong thwartive capabilities. It is a little emphasized fact of macromicrobial. interaction that, without any help from the much-vaunted antibiotics, mankind in a generation and through generations has emerged victorious against this or that microbe - fantastic feat by Nature at mass "immunization" or vaccination, allowing us to generalize that thwartive *reactivity is our license* to *sur*- vive.

The above is best illustrated by a few, justifiably lengthy, quotes from some leading works on microbiology: "In observing the progress of tuberculous infection, it is important to differentiate between that which occurs following infection of a person who has had no previous experience with *Mycobacterium tuberculosis* and that which occurs in a person who has previously been infected. In the former instance, there develops what we call primary infection or primary disease. In primary infection, one or more mycobacterial cells lodge within an alveolus where they are rapidly phagocytosed, most likely by alveolar macrophages. Because of their resistance to destruction, these virulent mycobacteria multiply within these macrophages almost as rapidly as they do in an artificial culture medium. However, since the maximum rate of multiplication is still slow, the increase in numbers of virulent tubercle bacilli will be slow. Therefore, the appearance of symptoms or pathologic condition due to the infec-tion may require several weeks. When the number of tubercle bacilli becomes significant, an inflammatory cellular exudate appears. Therefore, primary tuberculous infection is characterized by being pneumonic.

"In spite of the cellular reaction, there is little resistance to the multiplication of the tubercle bacilli, and soon after infection, dissemination from this focus occurs. This dissemination is primarily by way of the lymphatics, and there is early extensive involvement of the regional (hilar) lymph nodes. At the same time, there is spillover from the lymphatics

into the bloodstream with a seeding of virulent tubercle bacilli in all of the organs and tissues of the body. In a small proportion of persons thus affected, this process advances until widespread tuberculous disease, and possibly death, occurs, provided treatment is not given. In the majority of such persons, however, after a period of a few weeks the following dramatic changes are seen. The rate of multiplication markedly decreases, the pneumonic process resolves, and the dissemination of tubercle bacilli, to other organs ceases. The same changes also occur in all other tissues where tubercle bacilli may reside. Resolution of the disease process may proceed to a point such that, in many people so infected, little or no residue of the infection remains. In some, particularly in infants and children, all that may remain may be a Ghon complex; that is, a small calcified nodule in the lung and enlarged hilar lymph nodes.

"Coincident with the changes described above, two immunologic manifestation appear. First, the affected individual becomes tuberculin positive. In other words, he shows reactions of delayed hypersensitivity to certain low molecular weight proteins or polypeptides which are found in the tubercle bacillus. We have already noted that mycobacteria markedly promote induction of delayed hypersensitivity to other proteins so it is no wonder that they exert the same effect for their own protein constituents. Secondly, the macrophages within which the tubercle bacilli previously were able to multiply so readily now have acquired the ability to markedly inhibit the multiplication of virulent tubercle bacilli. Therefore, since the tubercle bacilli are now unable to grow within these cells, the disease process is arrested and, with time, many of the virulent cells are destroyed. In other words, the diseased person has now become immunized as a consequence of the reaction of his immunologic system to the infection. This type of immunity is known as acquired cellular immunity."[62] The foregoing drives home the evolution of thwartivity at individual (ontogenic) and group level. A passage from Dubos[15] renders clear the phylogeny of thwartivity: "Precise observations are available concerning the changes in the clinical manifestations of tuberculosis among some Indian tribes of North America. In

the first and the second generations to suffer from the tuberculosis epidemic in the Qu'Appelle Valley reservation, extensive glandular involvement was the rule in school-age children. Meningitis, generalized miliary disease, and bone and joint disease were extremely frequent - evidence of inability of the host to localize infection. In 1921, at a time when the generalized epidemic was in the third generation, the disease showed a greater tendency to localize in the lung and to exhibit a chronic course; the mortality was falling, and glandular involvement had dropped to 7 per cent among school children. This latter manifestation of high susceptibility to tuberculosis has continued to decline steadily and was seen in less than 1 per cent of children in the 4th generation. In other words, while tuberculosis among the Amerindians exhibited at first a very acute course, different in character from that observed in people who have had contact with the tubercle bacillus for several generations, now it is undergoing a change which makes it resemble the more chronic type of disease commonly seen among Western people under normal conditions." Antia[2] makes a comparable observation about mankind's thwartive resistance to the much-feared leprosy bacillus, the resistance having evolved over generations: "The human being is much less susceptible to leprosy than to tuberculosis or many other diseases; and even if he should develop the infection, about 80 per cent of the cases are self-healing."

Having presented the concept of *thwart*ivity - the arrestive cellulohumoral response by an organism against an actant (microbe, toxin, a graft) by which the organism was primed earlier - a few important generalizations on it are in order: (1) If *reactivity* against a foreign element can be described as a double-edged weapon, thwartivity represents the self-preserving edge, while combativity (combative reactivity) (see below) represents the self-destructive edge. (2) Apart from providing the faculty of wound healing, the CelluloHumoroVascular Reactive System is basically evolved and geared to provide thwartivity against the microbes so as to minimise reactive quarrels and the attendant dangers. Evolutionally, it has little to do with either tumor immunity or transplant immunity, either Robert Good or Christiaan Barnard. Immunity has nothing to do with the fetal

engraftment onto a mother. Maternal reactivity is concerned in this process, by being conspicuously kept out through means not yet understood, but sialomucin-coating of fetal trophoblast is the prime suspect. Sialomucin, or whatever the substance be, illustrates the principle[36] that *in Nature, functional necessity is the mother of structural innovation. (3)* Next to immunity, thwartivity represents the second line of defense mediated largely by the mopping macrophages (phagocytes) and the inactivating antibodies. (4) *Resistance is* another name for uncompromised immunity and/or good thwartivity, while *susceptibility* implies compromised immunity and/or poor/absent thwartivity. The state of resistance/susceptibility, in an individual, is determined by a dynamic balance that could change from hour to hour. (5) All forms of vaccination aim at induction of thwartivity, and often take advantage of cross-reactivity: Jernner successfully exploiting, in 1796, cowpox virus to thwart smallpox is a classic example;[14] others are the use of attenuated organisms (BCG) and toxoids. (6) Antimicrobial agents act by preventing/cutting short a reactive quarrel, hence affording thwartivity of a kind. Their extraneous nature and their multiple effects have been responsible for the dangers they pose. (7) Thwartivity may uncommonly be too severe - anaphylactic (truly, hyperphylactic), proving once more that reactivity is not an unmixed blessing. Generalizations (1) to (4) merit elaboration, as follows.

## Combative Reactivity

In absence of thwartivity, an organism enters into a regular combat - an eye for an eye, a tooth for a tooth - with the intruding microbe, and the result is not always good for the host. A reperusal of the large quotations above would show that both in ontogeny and in phylogeny, until such time that thwartivity develops as a force, combativity involves sacrifice of tissues or lives. Viral hepatitis, thanks to successful combativity and to the enormous regenerative power of liver, can mean a normal liver again, but during the acute quarrel, the host is on a precipice. The victory may sometimes be pyrrhic for the eventual outcome may be cirrhosis. Combative reactivity may pull the host out of tuberculous meningitis, but the aftermath may be bilateral ophthalmoplegia from

nerves paralyzed by fibrous engulfment. Like in day to day life, *a reactive quarrel averted, is a quarrel won.*

A stage in between good thwartivity and combativity (or a combination of the two) is the stage of chronic, but localized, inflammation or granuloma, where the protracted battle restricts itself to a focus without endangering the life or some vital parts of the organism. Reference to the quote from Dubos, above, will now amplify the significance of his statement that, "the disease showed a greater tendency to localize in the lung and to exhibit a chronic course." Most of the chronic granulomas represent this combination of combativity and thwartivity - the former unable to reach a definitive result in favour or against the host, the latter successful enough to contain the disease to a small area.

## Resistance versus Susceptibility

Often these terms are used in an abstract manner, but this conceptual vacancy can be mitigated in the light of our appreciating the nature of compromised immunity and/or nil/impaired thwartivity.

As was pointed out much earlier, a prime immunity mechanism is an intact epithelial cover. A large closed fracture may have an uneventful course but a small *compound* fracture may not, for in the latter case, immunity was compromised for want of a few epithelial cells. The modern therapy of "immunosuppression" involves the use of almost lethal cytotoxic agents that destroy epithelia from head-to-foot and inside-out., and it is then not surprising that the hitherto most harmless commensals turn into lethal pathogens.[43] The fault lies not with the pathogens but with the compromised immunity barrier. Cosmetics to decdorize the vagina may only lead to resistant vaginitis and candidiasis-a price paid for disturbing the normally operative mechanism. Lack of asepsis and antisepsis, in surgery, is a flagrant violation of the immunity barrier, an error that many an antibiotic may fail to rectify. The change of normal microbial flora, so common thanks to the modern antibioticism[28,42,43] can mean impaired immunity with resultant susceptibility. *Resistance,* in immunological terms, then means uncompromised immunity mechanisms - of every type and on every front.

The entry of a microbe into a virgin individual or a population is not resisted for want of thwartivity, with the result that a person, group or a generation appears as susceptible to the microbe, the *susceptibility* being expressed as combative reactivity with the odds often against the host. The susceptibility, however, changes into *resistance* with the evolution - individually, groupwise, phylogenically - of good thwartivity. On the other hand thwartivity, natural to an individual, may be impaired under varied conditions. Protein malnutrition may mean poor digestive enzymes right at the level of the scavenging macrophages so that the engulfed tubercle bacilli instead of being digested and eliminated, may multiply uninhibitedly[12] to eventually excite combative foci called clinically and pathologically as active tuberculosis. Hypercorticism, resulting from stress[33] or by medication, seriously impairs thwartivity, converting resistance into susceptibility.[28]

The foregoing discussion on *resistance/susceptibility* may drive home a point that in an encounter between a microbe and man, the latter may play a more decisive role in inviting/avoiding infection. Such eulogistic accounts of man's "success" against microbe as Paul de Kruif's *Microbe Hunters* and such anthropocentric labelling of microbes as "microassasins"[50] have fostered the idea, in minds medical and lay, that the microbes are the villain-of-the-piece. In reality, the *Homo sapiens* may be the greater villain. Such elaboration is pertinent in the present article for "immunity" from within[23] and antibiotics from without[50] have been hitherto held as "protecting" man against the microbial "enemy." The truth is probably different as follows.

## Microbes versus Man

In the heading above, ordinarily Man would have had the pride of place, but biorealistically he can't, for he is too puny in comparison with the Microbes: "Their prevalence is stupendous; it has been calculated that *by weight* they exceed all animal life on earth twenty times. Their *numbers* are incalculable and beyond comprehension."[21] Notwithstanding this awesome microbial dominance, clemency seems to be the rule, cruelty an exception. "By far the most common type

of relationship between an infectious agent and the host," Wood[58] generalizes, is of the "nondestructive' symbotic or commensal" variety. The human population explosion has had its start as early as 1400 A.D.,[59] much before Pasteur, Lister or Domagk had offered anything against the "micro-assasins." Man is, what he is, because *of* - *and* not despite - the microbes.

In interactional terms, the microbial plagues of the past were an outcome of man's alarmist[51] combative reaction against a particular microbe, this being man's initial *reaction* towards any microbe. Later, symbiosis prevailed, on the dawning of thwartive wisdom - the principle that a quarrel avoided was a quarrel won. This axiom had its most impressive application - "the greatest lifesaving achievement in medical history"[56] - in the simple practices of sanitation, antisepsis, and asepsis, Man's penchant for entering into a combat with a microbe has been, is, and will be his own undoing.

"The fault dear Brutus, is not in our stars but in ourselves." (Shakespeare). We must now realize that it is not the microbe that is pathogenic, but man's reaction to it that makes it so. Either every microbe is pathogenic, or none is. This has been stated very well in *The Biologic and Clinical Basis of Infectious Diseases,* published in 1975. In an early chapter, Youmans[60] points out that although we have so far regarded "pathogens" as microbes possessing some unique disease-producing power, it must be emphasized that such special pathogenic characteristics of microbes are probably the exception rather than the rule. "It is now recognized that many bacteria not ordinarily regarded as pathogens have the capacity to produce infection and disease, and this capacity will depend more upon host defense mechanisms than upon any special characteristics of the microbial cell."[60] Man, know thyself, and the limitations of the powers of thy "immunity", and antibiotics.

Antibiotics generate "immunodeficiency."[46] This they do by interfering with the macromicrobial dialogue, a necessary prelude to the emergence of effective thwartivity in an individual or a group. They also render a person vulnerable to other infections by upsetting the microbial flora. The

dangers they pose led Raeburn[46] to prophesize, in 1972, that "In years to come, the story of antibiotics may rank as Nature's most malicious trick" on man. Hardcore statistical facts more than support the above prognosis: Dubos[15] begins his chapter on microbial diseases with a cynical heading-"THE SO-CALLED CONQUEST OF MICRO-BIAL DISEASES," pointing out that despite so much blah blah on victory over microbes, paradoxically the percentage of beds occupied by patients suffering from infections is now as high as it was 50 years ago. A recent editorial[17] in the BMJ painfully generalizes that the mortality from cerebellar abscesses has risen from 25% in the fifties to 55% in the seventies despite all the antibiotics now available, and that today brain abscesses carry the same mortality as they did in the hands of Macewen in 1893. Paterson[42] concedes that antibiotics had, had their day, but the gains have been *more than offset by* a steady increase in the incidence of infections caused by microbes previously considered much less pathogenic or even non-pathogenic. Youmans too is justifiably cynical in attributing the foregoing to "Medical Progress". He concludes that while managing an intractable infection, what is needed is not the "right"antibiotic, but an understanding and the rectification of the disturbed macromicrobial interrelationship. No antibiotic, extant or on the horizon, could ever compensate for a combative focus that a ventricular shunt or a valve excites by the mere fact of being foreign, nor could it mitigate the cytotoxic ravage perpetrated by modern immunosuppressive advances. The unsurmountable problem of microbial resistance to antimicrobials is too self-evident to merit any detailing here.

The handwriting on the "immunological" wall is clear: Fleming and his followers have had a past, but Semmelweiss and Lister have a perennial future. The best "immune" response is one that is not needed, as a response or a reaction. Notwithstanding the eulogies by Robert Good-"the dominant figure of modern immunology"[49] - so-called "immunity" and "immune-reaction" are poorly trustworthy in man's battle against microbes. It has been customary to call the latter *parasites;* the truth is that microbes are *the* host, and man is but a guest in ' the microbial world. It will be a great day for mankind when "so useless" modern medicine will stop

bragging about antibiotics and antibodies, and come to ecological terms with the mighty microbes.[15]

## Summing Up

Biorealistic appraisal of the nature of "immunity" renders imperative. the. realization that the era of immunologism, Leleism (Immunity as everyone's: fool); and Goodism (Immunity can knock off microbes with one hand, malignant cells with another) should come to an end, the sooner the better. The swelltide of immunologismic arrogance has bred researchosis, papyrosis, and confusion worse confounded from unintelligible double-speak, all climaxed recently by "the scientific scandal of the century," the famous *la affaire de Summerlin* from the prestigious Sloan-Kettering Institute, New York.[49] Perusal of Burnet's[10] *Genes, Dreams and Realities* makes it painfully clear that the much-vaunted molecular biology is failing us everywhere to which immunology is no exception. The future of immunologic research is clear - there is no future. The discovery of "auto-immunity" has added a cancerous mass of facts, unlikely to make much beneficial sense vis-a-vis man and his maladies.

Immunity and reactivity are *gestalt* processes that, like most natural processes, permit wider understanding but little interference. Immunity is the liaison officer between the *self of* man and the *not-self* microbes, and sees to it that man keeps afloat in the microbial ocean. Reactivity is far more complex, but its *raison d'etre is* to recognize any disturbance in cytologue, react and reject the disturber be it from without or within, and finally to restore things to *status quo ante.* No wonder, then, that aseptic inflammation, septic inflammation, "auto-immunity," wound healing, graft rejection or the rejection of an implanted glass piece, one and all, evoke basically the same Cellulo-HumoroVascular Response.[65]

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Editorial

# Integrity, Immunity, Reactivity, Restorativity: Biolessons off Brain Abscess

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**Manu Kothari,[1] Atul Goel[2]**

A brain abscess (BA) as an ensconced pocket of pus is no more no less than an abscess on the toe or the torso. It begs to be drained along the Hiltonean maxim: *wherever there is pus, let it out*. It is BA's deep and 'dangerous' location that needs diagnostic and operative wizardry comprising THEOS-SLAM-AAAA.[1] THEOS (=religion) implies Technicized High Element Of (Diagnostic) Suspicion. SLAM - meaning winning all the tricks of the game - reads as Speedily Locate, Adroitly Manage, by AAAA- Aspiration and/orAblation, Antibiotics and Antiepileptics. What biolessons could BA offer?

The term *intelligence* connotes 'reading between the lines', from *inter* = between and *legere* = to grasp, read, choose, pick up. BA's acknowledged uncommonness, bordering on rarity illustrates the *immunity* that the neuraxis exhibits against patently pyogenic microbes. The evolution and nature of BA manifests brain's reasoned *reactivity*, or mindful *munity*. The alacrity with which BA responds to timely measures exhibits the animal body's *restitutivity* or *restorativity*. And encompassing these three bioforces and a lot more is *integrity*. It is time that these bioforces comprising *Vis Medicatrix Naturae* - the Healing Power of Nature- were brought into a broader relief.

1. Ex Professor Department of Anatomy, King Edward Memorial Hospital and Seth G.S. Medical College, Parel, Mumbai, India.

2. Professor and Head of Department of Neurosurgery, King Edward Memorial Hospital and Seth G.S. Medical College, Parel, Mumbai, India.

Macfarlane Burnet got his Nobel in 1960 for concepts that spawned the idea of body-cells as 'self' rejecting anything perceived as non-self. In 1962, Burnet published a mini-classic *Integrity of the Body*, wherein he evolved the idea that the chief function of the animal immune system is to keep intact the body's integrity or wholeness by rejecting whatever that is alien to it.

In *Cellular Immunology* Burnet interestingly observes: "Primitive neurons seem almost to be programmed individually, each to move and direct its axon (and dendrites) along an elaborately predetermined course". If even a single of the billions of neurons knows where to place itself during and after embryogenesis, then surely each of the 100,000 billion body-cells, coming off a single zygotic cell knows where to place itself, how and how long, given its place in a cytogalaxy where no two cells are riveted or pasted to each other and yet all stay put from conception to cremation, without denying rapid travel throughout the body to many a cell-type. *Integrity* is an animal's total noumenal blueprint that precedes, accompanies, and succeeds the animal body and one which knows how far to heal a wound or a gap whereby the body is restored to *status quo ante* as near to the original as possible. Multiple aphthous ulcers in the mouth, needing billions of cells to repair, get healed impeccably, and smoothly, leaving no rubble strewn around. Ditto for the BA, single/multiple, small/large, of whatever origin, *integrity* orders reactivity and restorativity to so work that the least of the brain remains compromised after the BA has been therapeutically dealt with.

Given the long and ever-expanding list of autoimmune disorders, modern medicine knows not whether immunity is a friend or a foe! Medawar, the co-Nobelist with Burnet, sums up the perverted parlance of immunology as barefaced and silly, whereas Glemser, a US journalist, sizes up modern medicine's predicament by his generalization that the science of immunology is so advanced that one immunologist can't comprehend what another is talking about. Some principled parlance is in order.

*Munis* means duty/service. *Im* - in immunity is negation, and implies freedom from service, or from having to work.

Immunity, then, means nonreactivity or absence of munity. The Burnet-Medawar symphony played the tune that the human embryo, *circa* fourth month of intrauterine life, eliminates from its thymus clones that could possibly react against the body's cells and elements. Thereafter, the so-called immune system knows which part of the body is self, and what is not-self. A self-marker or a suimarker is endowed to each self-element, an advantage not denied to an alien unit or cell present at the time of thymic maturation. Hence the acceptance of grafts, experimentally, or in monozygotic/dizygotic twins sharing a placenta, between individuals so involved. Immunity, in its principled, etymologic sense is aristocratic nonreactivity. Brain, as a tissue, is notorious for not reacting to deliberately inoculated organisms. Hence, the rarity of BA despite so much of otitis, sinusitis, septicemias and pyemias. BA illustrates immunity by choosing not to occur, despite the all too common head-injuries, involving a lot of road muck getting into the brain, with bony sequestra strewn around.

The word *munity* is best understood by the close parallel between immorality *versus* morality, and immunity *versus* munity. Munity, allied to munition or arms, is synonymous with reactivity of the animal body against non-self elements. The arsenal comprises cells and humors (antibodies), and the system is best acronymized as CHRIST - Cellulo Humoral Reactivity Insuring Somatic Totality.

As and when the brain *has* to react against a microbial alien, the reactive or munitive forces set up a focus of inflammation (cerebritis or cerebellitis), followed by the creation of a barricade all around to form the so-called capsule of the abscess, that now lyzes body's leucocytes and co. to create a fluid-focus called an abscess, that expanding hydrodynamically is capable of finding its way to the exterior, a phenomenon as common amongst humans as amongst animals. But in the case of BA, the walls that it must penetrate through are the vital and fragile brain tissue itself. So BA asks the fibroblasts of the vessels in the capsule-wall to generate enormous armor of collagen - collagenization - that permeating the abscess makes BA into more of a tumor than a fluid-filled abscess, more of a pyoma than a pyocele, and a

pyoma so discreetly separated from the brain tissue around, that a pyomectomy can be carried out with ease, given the plane of cleavage that separates the BA from the rest of the brain.[1] It must be clear to us all that CHRIST when operative in BA exercises reasoned-reactivity, and mindful-munity, whereby the BA, indistinguishably behaving clinically and radiologically as a tumor, alerts the patient and the clinician into the triad of THEOS-SLAM-AAAA, assuring thereby rapid recovery. Even a BA thinks, reasons, and reacts to assure minimal brain damage, and rapid, maximal recovery.

The reactivity attending BA has had to be honored as reasoned, for the forces of CHRIST, of reactivity, are enormous. One has just to think, on the one hand, of severe SLE, a form of contra-auto-reactive-syndrome (hitherto called autoimmune syndrome), and relentless graft-rejection on the other to appreciate the power that CHRIST can, and does, wield. It is, to use the framed phrase of Lord Tennyson, *Nature, red in tooth and claw.* The reasoned nature of CHRIST is BA, and so often as elsewhere, it is functioning integrity, that converts CHRIST into a vector imparting to it direction, magnitude, modes, and a switch-off. Once the alien contents of an abscess cavity or the abscess itself are out, what is left is a mass of native neuraxial and guest reactive cells, all self, and hence no longer in need of any more reactivity. So hereafter, what sets in is the restorative or restitutive power of the animal body, *albeit* under the all-seeing eye of integrity.

An Oxford dictionary synonymizes the Latin phrase *restituto in integrum* as restoration to the uninjured state or restoration of the *status quo ante*, meaning the previous position. Be it bone, brain, bone-marrow, or liver or lung, integrity, having for itself the original blueprint of the body, orders the restorative powers to aim at reducing the area of injury/inflammation/wound/abscessing to its barest minimum, and then offer secure repair to almost original state. In BA, once the abscess contents/abscess itself are out, the remaining neuraxial tissue, or the walls of the BA that has been aspirated, set about working to leave behind, at the most, a fibrous cicatrix, that calls for antiepileptics for a year or two. Needless to say that integrity imparts to restorativity direction, magnitude and components and a switch-off as it does to

reactivity. If a liver is excised 25%, restorativity goes into action to replace whatsoever liver has been lost, no more, no less. In the neuraxis, neurons lost are lost forever. Yet integrity strives to replace the gap by reactive gliosis if need be. The attempt all the time is to restore the integrity of the brain to *status quo ante.*

The rarity of BA is turning into its commonness because of modern therapies 'immunocompromising' the patients, young and old. Here you see a paradox. On the one hand, you claim suppression of immunity as responsible for the setting up of inflammation, abscess, pus, *et seq*. On the other hand, these events proclaiming the active manifestations of the forces of 'immunity' occur widely in the body and the brain. In reality, there is no immunosuppression, or, more correctly, reactosuppression or CHRIST-letdown. What is at stake is the compromised skin/mucosal lining, because of the indiscriminate cytotoxic nature of the so-called immunosuppressors. The result is SICKness- Structural Integrity Compromised Kemically, a state that drives the innocent bacterial symbionts deeper into where they ordinarily never are. The body has no other recource but to request CHRIST to go into action to set up BA and what have you. Unless the body has enough reactocytes (immunocytes), how would even an abscess form! SICKness opportunizes the innocent microbes which then get condemned as opportunistic. To borrow Shakespearean felicity, "The fault, dear Brutus, is not in our microbial-friends, but the compulsion to which they are iatrogenically subject". The pancytotoxic nature of the therapeutic immunosupressors also knocks out the elements of bone-marrow thus accounting for the various hemocytopenias. One can generalize that BA is more due to SICKness, than due to suppression.

BA is a good teacher. We better learn a lesson or two from one of the Nature's wonders called BA.

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Original Article

# Brain Abscess: A Cogent Clarifier of the Confused Concept of Immunity

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**Manu Kothari, M.D.[1], and Atul Goel, M.D.[2]**

*Abbreviation used in this paper:* CSF = cerebrospinal fluid.

## Abstract

The brain tends to be immune to inflammation and abscess formation, despite chronically and recurrently infected neighboring structures, and not uncommon pyemias and septicemias. Experimental inoculation of the brain tissue with microbes confirms this clinical experience. When brain–microbial interaction overcomes immunity, reactivity sets in, resulting in inflammation and abscess formation. Brain abscesses tend to stand apart from the host tissue so as to allow easy aspiration and/or ablation. A brain abscess is a dire neurosurgical emergency. The saving grace is that a few quick steps yield excellent results.

## Introduction

Experimental data suggest that the neuraxis is remarkably resistant to infection.[26] The brain is resistant to abscess formation.[29] With microbes triumphantly resistant to powerful antibiotics; with often fatal pyemias and septicemias rampant the globe over; with children in third-world countries experiencing head-region pyoderma often caused by bilateral purulent otitis media; and with paranasal sinuses, which are

1. Ex Professor Department of Anatomy, King Edward Memorial Hospital and Seth G.S. Medical College, Parel, Mumbai, India.
2. Professor and Head of Neurosurgery, King Edward Memorial Hospital and Seth G. S. Medical College, Parel, Mumbai, India.

also paracranial, recurrently full of resistant pus, the cool assertion of the brain's immunity to abscess formation arrives as a welcome surprise. A leading, intellectually jarring note, marring this celebration, is the spate of specialty papers, clinical as well as experimental, in which authors consider immunity itself as pathogenic in brain abscess—a "j'accuse" that perpetuates the confusion even more.

One definition of the term immunity—from im (not) and munis (service) (hence, municipality)—is "exemption from public service, especially military service." Immunity implies worklessness. No wonder, until today, those active in modern medicine have not known whether immunity is a friend or a foe.[16,17]

Immunity, as a concept, has yet to be defined. Medawar, the co-Nobel Prize winner with Burnet, has described immunology as ailing from "bare-faced empiricism and embarrassingly silly terminology." Immunity, it would seem, is a force that runs with the hare to hunt with the hounds, a situation reminiscent of the Big Brother in Orwell's novel 1984: "He was the tormentor, he was the protector, he was the inquisitor, he was the friend." Immunity-wise, Nature seems diabolical.

Nature is not malicious, provided we differentiate immunity from reactivity.[16,17] Immunity, in its quintessence, is an aristocracy of being that refuses to react to a situation, avoids a showdown or a fight, and lets irritants pass by. Reactivity is the body's reasoned reaction to an antigen, microbe, graft, and so on. The brain is aristocratic enough to exhibit lofty immunity, but when need be, partakes in reactivity that spawns inflammation, pus, and abscess. Even in such cases that it capitulates, there is method in the brain's seeming madness: pre-gnomically, BRAIN reads Balanced Reactivity And Immunity Noticeable—a judicious mix of the body's bittersweet while dealing with the ubiquitous microbes.

Ropper and Brown[27] have written, "In most instances of bacteremia or septicemia, the nervous system seems not to be infected…. With respect to the formation of brain abscess, the resistance of cerebral tissue to infection is notable…. The arachnoid membrane (in fulminant meningitis) tends to serve

as an effective barrier to the spread of infection into the brain substance…. Only rarely does acute bacterial meningitis result in a brain abscess." Thus, the brain can wear an intimate garb loaded with virulent microbes and yet stay clear of them. The brain in fact has learned this trick from the human body. "As many as 100 trillion viruses and bacteria live on each of us. However much we wash, there are always ten million or so bacteria on every square centimeter on our skin."[1] The human body has $10^{12}$ number of cells and $10^{13}$ number of microorganisms. This blanket of life covering our skin and mucosae is the human body's "surfinsic/surferior" milieu, endowed soon after birth and symbiotically coexisting with each one of us unto the grave.

If, as Lovelace wrote in the 17th century, "stone walls do not a prison make," then the loads of microbes painting our surfaces do not infection beget. Massive microbial symbiosis is the hallmark of human health. The ability of the human body to live in peace with 10 microbes per every human cell is a state of genuine immunity, wherein the body exercises a holy indifference to the resident microbes, to gain therefrom freedom from any reactivity against the obviously non-self microbes. The joint Nobel Prize winners (for discovery of acquired immunological tolerance) Burnet with Medawar brought to the fore the realization that the so-called immune system reacts against any element it perceives as non-self, through a wide assortment of cells ("reactocytes") and humors ("reactins"). The reactivity cascade, by and large, results in the rejection of the non-self focus.

Burnet has extensively elaborated on the fact that the human immune system is not so much antimicrobial as it is anti–non-self, for the integral body is uninterruptedly comprised of self-units that dialogue with one another to hold a 10-trillion cell economy into a gestalt whole without any screws, tape, or adhesives.[5–8] Cells and fluids move with stellar ease in the individual body-universe.

A non-self focus can arise from without and/or within. A surfinsic virus/microbe/fungus can turn intrinsic through a breached epithelial barrier. A splinter or thorn may serve the same purpose. A wound, small or large, would contain

damaged/dead tissue of one's own but no longer self. Thyroid or, say, gastric cells, may mutate to pose as non-self. A grafted kidney is a large non-self locus. The body's reactive repertoire[16,17] contends with each of the aforementioned in a prototypical way: Recognize, React, Reject, Repair, and Restore to status quo ante as best as possible. The vector assembly to achieve this is CelluloHumoral Reactivity Insuring Selfsame Totality, or CHRIST for short. Little wonder that processes as diverse as microbial infection, wound healing, graft rejection, or the so-called autoimmune phenomenon are mediated by what we call, for want of any kinder term, inflammation, eulogized by Nobel Prize–winner Florey as "the backbone of pathology." Inflammation, a gift from CHRIST, is the animal body's greatest invention and one's only license to survive the rough and tumble of life, manage severe infections, heal massive traumatic/operative wounds, and peremptorily throw away well-intended but non-self grafts. The fact that the human body exhibits no reactivity to, much less rejection of, one's own cancer proves that cancer is part of the self. No wonder, Maclean[20] qualifies a cancer cell as a "superdifferentiated normal cell." The massive drug market for antiinflammatory agents reflects medicine's poor appreciation of the inflammatory gift and is tantamount to crucifying CHRIST. It is the same for an angel called pain. It would be no exaggeration to see Inflammation and Pain as the twin guardian angels of the human body.

Abscess and pus are the children of inflammation and, like Quasimodo in *The Hunchback of Notre Dame,* have a bizarre demeanor but a heart of golden benevolence. Both abscess and pus are discussed pejoratively and, therefore, stand forever condemned. In abscess, abs (away) and cess from cedere (to go) connote something that goes/drains away. From Skt. puyati (to stink) comes the word "pus," meaning something foul, putrid, or rotten. If, in the famous Hollywood musical *My Fair Lady,* Mr. Doolittle, the lovable rascal and father to Eliza, had to have biological clarity, he would have described his own abscess and pus as "Me own flesh and blood."

Let us now picture how abscess and pus, the two powerful arms of *Vis Medicatrix Naturae* ("the natural curative power

inherent in the organism"[9]) work. The CHRIST detects a splinter, a modicum of microbes, or a bit of dead tissue and sets into motion "cellulohumorovascular" reaction to occasion the classical Celsusian signs of inflammation[10]—namely calor, rubor, tumor, dolor, and the Galenical functio laesa. If the inflammatory cellulitis cannot dispose of the non-self focus, CHRIST sets about throwing a fibrous barricade—the wall of the upcoming abscess. The CHRIST knows that the only way to discharge the non-self focus to the exterior is to spawn a fluid-filled cavity, under tension, by, if need be, lysing the patient's own tissues. Just as the solid fetus is delivered after its bag of water dilates the maternal passage, so does the fluid-filled abscess strive to find a path to the exterior, throw away the non-self material, and then heal the gap left behind. Even a brain abscess is known to have spontaneously healed this way. To make the saga complete, it pays to study the typical composition of pus: "A liquid inflammation product made up of cells (leukocytes) and a thin fluid called liquor puris."[9] The brain, in its innate wisdom, largely denies itself the hydrodynamic option of a fluid-filled tense cavity, making the abscess focus more solid than fluid because the brain knows that any such venture could direct the abscess to burst into a ventricle (IVROBA) with disastrous consequences. The brain prefers a pyoma to a pyocele, and a mycoma to a mycocele.

Incidentally, brain abscess, more as a pyoma than a pyocele, is best suited to underscore the dual definitions that the word "abscess" enjoys.[28] In Celsusian sense, apostem/apostema/aposteme is abscessus (a pyocele). However, Marcus Aurelius Severinus used "abscessus" to connote a tumor or new growth, not excluding cysts. The universally established resectability of a brain abscess can be summed up as a pyomectomy and, likewise, mycomectomy.

Having glimpsed the raison d'etre of the 2 bioinventions called pus and abscess, it is now time to allow the brain abscess itself to turn into a teacher that helps medical science distinguish immunity from reactivity.

Let us focus on the so-called immunology of brain abscess. An extensive review charges "inappropriate glial activation"[13]

as perpetuating antibacterial immune response that ends up contributing to disease pathogenesis. Another extensive review[5] holds them responsible for both defense against, and neuropathogenesis of, central nervous system infections. The review concluded, "The evidence to date suggests that activated microglia functions as 'double-edged sword' with neuroprotective features predominantly in the healthy nervous system and neurodestructive properties observed in various states."[25] Because the review does not explain the neuroprotective features of microglia, the microglia end up being neurodestructive in conditions as apart as abscess and Alzheimer disease. Microglia—the immunocytes of the central nervous system—run with the hare and hunt with the hounds. Bengalese writer Rabindranath Tagore bemoaned, "We read Nature wrong, and then blame her." The truth is that immunity, true to its meaning, is an innate, lofty, nonreactivity that thrives on the principle that the best battle is one (or won) that is never fought.

Any thing or event from without and/or within that breaches the self-same cellular continuity of the body gets vigorously addressed by cells and humors generally called immunocytes and antibodies. The non-self is eliminated and self-sameness is restored through what can be called reactivity. Reactivity entails fever, inflammatory cellulitis, pus formation, abscess formation, and graft rejection, all seen through medical eyes as "abnormalities" to be treated, nay, combated. "In the years to come," Raeburn[24] mused, "the story of antibiotics may rank as Nature's most malicious trick" on mankind, ushering in unintended immunodeficiencies. Reactivity, like pain, is our license to survive, nay thrive, and does so with the sole aim of sustaining the human being.

A brain abscess is a brilliant illustration of the coexistence of immunity and reactivity, the former striving to stay away from the abscess and the latter fighting to do its very best to save the precious neuraxis. Let us detail how.

## Toward a Synthesis of Immunity, Reactivity, and Brain Abscess

The infrequency of brain abscesses in the midst of microbial

crisis, locally, focally, or systemically reflects the brain's immunity to abscess formation. When an abscess *does* develop, however, the various processes that go into making and manifesting it comprise the brain's reactivity. An expanded appreciation of the following may help a neurosurgeon understand why an abscess does not occur and when it does, how and why, as well.

## The What and Why of the Brain's Immunity to Abscess Formation

First, the brain—as the experimental psychologist R. L. Gregory said, "like nothing so much as a lump of porridge"—is innately strong. Ropper and Brown[27] have written, "Direct injection of virulent bacteria into the brain of an animal seldom results in abscess formation. In fact, this condition has been produced consistently only by injecting culture medium along with the bacteria or by causing necrosis of tissue at the time bacteria are inoculated."

Second, the brain's immunity to abscess formation is 2-fold: it is so despite intimate contact with inflamed and infected arachnoid (vide supra), and it is so despite direct planting of virulent microbes into its substance.

Third, a leading reason for the aforementioned nonreactivity is that the whole neuraxis, during embryonic ontogenesis, "escapes" tolerance in the thymus, thus acquiring "immune privilege," which suggests the neuraxis' ability to ignore reactive (antigenic) stimulus in the form of microbes.[21]

Fourth, as Male and colleagues[21] have written, "Immune privilege is clearly designed to dampen down inflammatory responses in certain vital organs. The same suppressive mechanism would apply equally to inflammation caused by infectious or self-antigen." Both the third and fourth points support the brain's deliberate "nonreactivity," heretofore incorrectly called "immune privilege" for privilege as a word could mean indulgence, irresponsibility, and unaccountability, and hence access to hyperreactive/inflammatory response.

Fifth, neurons, like muscle cells, belong to the category of

perennial/immortal/postmitotic cell populations wherein cell multiplication ceases soon after birth.[18] The cells tend to be very large. Both nondivisibility and large size endow nonreactivity.

Sixth, the endothelium lining the entire neuraxial vasculature-neuroangiothelium—exhibits special features that earn for it the exalted status of blood-brain barrier, also now called "neuraqua endothelial audited/selective transport" (NEAT/NEST).[15] The widely acknowledged fact that neuraqua (the CSF) remains unaltered/unhelpful in a fait accompli brain abscess implies that the blood–brain barrier and NEAT/NEST are not restricted to the choroid plexus but rule the entire neurangiothelium.

The aforementioned constellation of factors, and many more yet to be fathomed, underlie the brain's immunity, and help to make sense of assertions such as the following: "Brain abscesses are extremely rare in septic conditions such as pyelonephritis, pneumonia, and vascular catheterization."[2]

## The What and How of the Brain's Reasoned Reactivity While Abscessing

> Though this be madness,
> Yet there is method in it
>
> **William Shakespeare**
> *Hamlet* (Act II, Scene 2)

A leading microbiology text sternly warns us: "Untreated brain abscesses are fatal. Surgical excision provides the initial therapy as well as diagnosis of brain abscess."[4] The surgical success has been underscored neurosurgically[19] by the generalization that "the method of surgical treatment (aspiration and/or excision) is of less importance than adherence to the basic principles of surgical management," whereby the brain abscess, whether single or multiple, unilocular or multilocular, offers equal therapeutic reward. This oft-sung success of surgery in an intimidating condition called brain abscess, even when the lesion is fungal, holds true despite the fact that modern medicine's strong drug

arm—antibiotics—is recognizably limp. That antibiotics need not have played, nor do they need to play, a pivotal role is amplified by the surgical success[11] against brain abscess as far back the end of the 18th century: in 1893 Macewen reported results that bear favorable comparison with any modern series. His subjects included 10 patients with temporosphenoidal abscesses, 8 of whom survived; all underwent mastoid operations, 2 had a cerebral abscess evacuated via the mastoid approach, and 6 via a temporal trephine disc. The patient history of neurological dysfunction varied from 1 week to 1 month and, therefore, chronicity cannot be the sole explanation of his success. Moreover, 6 of his patients had level D consciousness on admission. The English success had had a contemporary in the then Ottoman Empire in 1891.[23]

The consistent success of surgery, in brain abscesses, in the pre-antibiotic/antibiotic/antibiotic-downslide era is clearly the result of the nature of brain's abscessing, through the recognizable reasoned reactivity shared by CHRIST on the one hand and the brain itself with its neuroglia on the other.

## THEOS-SLAM-AAAA: the Triad Assuring Success

A global survey of the surgery of brain abscess, 1891–2008, would drive home the relevance of the aforementioned acronymic triad. In this triad, THEOS (meaning religion) stands for Technicized High Element Of Suspicion—the moment you suspect, use all technical modalities till you hit a SLAM (meaning winning all the tricks in the game) connoting Speedily Locate Adroitly Manage. The simple-looking CSF examination fails to help for 2 reasons: it chooses to get unaffected, and a thoughtless tap could precipitate herniation. A quartet of adroit management is Antimicrobialize, Aspirate, and/or Ablate and over an extended time Antiepilepticize. Needless to say, THEOS-SLAM-AAAA comprises "the basic principles of abscess management."[19]

The first A in AAAA, for want of any sensitivity-guidance, has to be a strong cocktail led by penicillin, and fortified by others, including metronidazole. The second A may entail repeated aspiration under image control. The third A is capable of

teaching a neurosurgeon that the oma-like abscess tends to be isolated from brain tissue and lends itself to ready enucleation. The fourth A is a protracted must. The first 3 *A*s must be in hurried succession. The antimicrobial cocktail gets replaced by a specific one on identifying the visitor. The factors that almost conspire to help the patient and the surgeon comprise some self-evident truths as follows.

## Incidence: Amazingly Low

"The incidence of brain abscess has remained stable in the antibiotic era; nevertheless it is generally regarded as a rare disease, with large autopsy series reporting an occurrence rate of 0.18 to 1.3 percent…. brain abscess remains a significant problem in the developing world, particularly children living in poverty…. male:female ratio of 2:1. In some series, brain abscess secondary to otitis media displays a bipolar age distribution, with peak in children and after 40. In contrast, brain abscess secondary to paranasal sinuses usually occur between 10 to 30 years of age."[26]

## Routes: Continuity, Contiguity, Circuity, and Crypticality

Direct, clear continuity between pathogen(s) and parenchyma produces poor abscessing. No wonder, despite their enormous numbers, head injuries and procedural/operative trauma remain immune to abscess. Contiguity accounts for the largest number of brain abscesses, neighbored, as the brain is, by usually infected paranasal sinuses and the commonly infected middle ear. The brain's infected neighbor decides which part of it abscesses. Otogenic brain abscesses are most commonly located in the temporal lobe or cerebellum; conversely, 85–95% of cerebellar abscesses are associated with ear or mastoid infections. Usually these lesions are solitary.[26] Little wonder the occipital lobes, for want of an infected neighbor, never abscess by continuity.

The brain's circulatory oneness with the rest of the body renders it susceptible to abscessing in pyemia, septicemia, fungemia, lung abscess, pelvic infections, and so on. The immunity—nonreactivity—that neurangiothelium exhibits against widely circulating microbes accounts for the freedom

that the neuraxis enjoys. In 15–20% of the cases the brain abscess is cryptic—that is, you cannot guess the source. Presumably the route is vascular, often an undetected periodontal sepsis.

## Sources and Species

In an order of decreasing frequency, brain abscesses are rhinogenic, otogenic, hemogenic, and cyanogenic. Cyanotic heart diseases presumably devitalizes the neuroangiothelium rendering the brain susceptible to abscessing.

Since the brain abscess behaves in a prototypical fashion throughout the course of disease, details on the menagerie of microbes that visit the brain singly or severally remains an academic issue.

## SICKness of Compromised Immunity

The tandem terms immunocompromised and opportunistic microbes beg for clarity. How come an immunologically depressed person develops multiple abscess, elsewhere and in the brain, to paradoxically exhibit intense "immunoreactive" processes in the form of abscessing, and so often by fungi. The reality is that the culprit microbes are not opportunistic, but are "opportunized" by the loss of surface integrity, largely because of drugs, be it in cases of cancer, transplantation, or AIDS. The "opportunization" starts with the person's Surface/Somatic Integrity Compromised by Khemicals, a SICK syndrome wherein the culprit is hardly the microbe. Even then, whatever the abscess(es), the response to therapy is highly satisfying, a credit more to the brain's balanced immunity and reactivity.

## Clinical Features: Cold Abscess, Hot Tumor

The clinical course of a patient with a brain abscess may range from indolent to fulminant; however, the duration of symptoms is $\leq$2 weeks in about 75% of patients. In most cases, the prominent clinical manifestations of the brain abscess reflecting the expanding intracerebral SOL are often nonspecific and depend on several variables (for example, the virulence of the infecting organisms, the patient's immune

status, the location of the abscess or abscesses, and the presence or absence of associated meningitis or ventricular rupture). Only a minority of patients exhibit the classic triad of fever, headache, and focal neurological deficit.[26]

A brain abscess epitomizes focally fast-growing pyoma (which begins manifesting signs at the stage of cerebritis), a locale that is poor in reactivity (hence often sterile, uninformative CSF), and an unexplainable absence of systemic reactivity in terms of fever, leucocytosis, erythrocyte sedimentation rate, and C-reactive protein. Such a contrast may be present in as many as 50% of cases. However, all the symptoms and signs of SOL abound.

Compared with a cytoma (brain tumor) that is tardy in its growth, a brain pyoma/mycoma marks the rapidity of its expansion in terms of days. Any delay may mean disastrous coning or IVROBA. One can thus sum up brain abscess' clinical picture as one of Cold Abscess, Hot (volcanic) Tumor. It is like a fire in an oil well, and all that you can do you must do at your speediest.

## Teleological Pathogenesis: Obliging Oma

*From the Greek word for goal, task, completion or perfection. Teleological explanations attempt to account for things and features by appeal to their contribution to optimal states, or the normal functioning, or the attainment of goals, of wholes or systems they belon*g to.[12]

Needless to emphasize, the pathogenesis, whatever it is, is not immunopathogenetic, but "reactopathogenetic." Brain abscess exhibits, when single/multiple or unilocular/multilocular, 4 stages and 5 zones. Such an "idealized"[26] picture is not always present, but it allows a working description of its evolution.

The 4 stages are early cerebritis (or cerebellitis), late cerebritis, early capsule, and late capsule, each discernible on neuroimaging. The 5 zones are: 1) a well-formed necrotic center; 2) a peripheral zone of inflammatory cells, macrophages, and fibroblasts; 3) a dense collagenous

capsule; 4) a layer of neovascularity associated with continuing cerebritis; and 5) reactive astrocytes, gliosis, and cerebral edema external to the capsule.[3] The denseness of the capsule is purposive. The final, or capsule stage, occurs from Day 10 onward and is associated with a well-vascularized abscess wall, in effect sequestrating the lesion to protect surrounding normal parenchyma from additional damage.[14] The plane of cleavage between Zones 4 and 5 forms the bedrock of excisional ease and success.

The reactive wisdom shines out through 2 very discernible features. The denseness of the capsule is the result of "an abundance of reactive collagen"[26] that is produced by fibroblasts derived from the walls of blood vessels.[10] The other teleological feature is that on the inner side of the capsule, and hence within the abscess, are the inflammatory cells, macrophages, and fibroblasts, whereas external to the capsule and separated from it by edema are the reactive astrocytes.[3]

A vascular explanation has been generally advanced that the capsule tends to be thicker on the side of gray matter and relatively thin on the white matter side, because of the greater vascularity of the gray area. While this may well be true, sight should not be lost of the fact that the abscess guides itself in such a way that it chooses not to invade and not to rupture into the neuronal layers of the cortex. The price that it exacts is that the thinness renders the abscess able to advance toward and rupture into the ventricle.

The tenacity of the wisdom of the abscessing brain comes from a study entitled, "Improved survival in central nervous system aspergillosis: a series of immunocompromised children with leukemia undergoing stereotaxic resection of aspergillomas."[22] In each child reported in this series, and in every abscess, successful image-guided resection of the lesion was possible. "Complete resection of the abscess yielded gross findings of a viscous fluid contained by a firm rubbery wall surrounded by soft capsule."[22] Even under SICKness (vide supra), the brain retains its balance between innate immunity and reasoned reactivity.

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# TRAS principles blight arterial bypass and plasty.

**Kothari MV, Mehta LA, Kothari VM**

Department of Anatomy, GSMC and KEMH, Mumbai.

**Correspondence Address:**

Department of Anatomy, GSMC and KEMH, Mumbai.

## :: Abstract

A new concept--Tissue Requisitions (Principle I)/Relinquishes (Principle II) Arterial Supply--of TRAS principles is introduced to help appreciate the failures/successes of modern medicine's attempts at restoring arterial flow in luminally compromised coronary/carotid fields, an invasive branch rightly called vascular ReRheology, which comprises diagnosing/treating arterial blocks. The technical wizardry of arterial reconstruction (bypass) or lumen--restoration (plasty) has to reckon with the TRAS principles all the time.

Key terms: Coronary, carotid, bypass, angioplasty, TRAS principles, ReRheology.

Diseases of aging are rightly called chronic for they are spawned by chromos or time. One of its important manifestations is luminal loss because of various processes resulting in compromised flow of air/food/fluid/feces along the body tubes. Deoccluding the lumen is an attempt at restoring the *rheos* or the flow and thus deserves the new name ReRheology. Coronary ReRheology is a global superspeciality that thrives on ultrasophistication of gadgets and procedures that refuse. It is needless to emphasize that the other branches of ReRheology are biliary, intestinal urinary, genital and so on.

Coronary-to-the-heart and carotid-to-the-brain commonly exhibit concurrent pathological changes of atherosclerosis or arteriosclerosis. The arteries become thickened. Most importantly their lumen gets narrowed thus “denying” to the heart or the brain its due share of blood. the analogy of a blocked pipeline  as the villain-of-the-piece is so compelling that delineating the block in the course of blood and then getting rid of the block have become the ready solutions to any obvious problem.

The straight-line-solutions of deblocking the highly accessible carotid arteries by bypass, endarterectomy, angioplasty, reaming and what have you has refused to yield expected results. The obstinacy with which poor results and inevitable complications occur has led most therapists to give up any surgical or gadgetic interference with the carotid.

On the coronary front, coronary antiography has been one-upped by the latest IntraCoronary UltraSonography. This technique allows, literally, direct visualization of te coronary vessels thus allowing the therapist to pick and chose a procedure.

**Coronary Is Blocked The Coronary Must Be Deblocked**

To a patient, to the next of his kin, to the medical student, journalist, and of course, the doctor nothing appears more rational than to go down and deblock the coronaries by reaming, endarterectomy, angioplasty, bypass, laser and to prevent the reblocking by an inlaid stent.

Providentially, the coronary vessels that suffer blockage are all extracardiac – meaning that their diseased segments course over the surface of the heart and hence are eminently accessible to whatever the procedure. Such "designer-blocks" are further helped by the fact that branches of coronary tree that run into and through the walls of the heart remain essentially plum normal.

Yet the biggest snag faced by coronary revascularization is the fact that medical science does not know if this magic really works. Hence the recent clamour for controlled trials.

The compelling need[1] for controlled trials to evaluate the therapeutic worth of such manifestly mechanical procedures as angioplasty and bypass speaks volumes for the tantalizing tentativeness that plagues them. It is a tacit admission of the distinct likelihood of the mindset of the doctor and/or the dis-eased triumphing over what really matters.

(a) Angioplasty is a euphemism for the forcible, mechanical tearing of a coronary vessel[2]. A natural consequence is AIDS – Angioplasty Induced Defiant Stenosis. Typical of allopathy's penchant for creating a problem and then setting about solving it are the experiments afoot towards tampering through genes and chemicals, the natural reactions of coronary tissues to the angioplastic insult.
(b) After over 3 decades and over a million bypasses, allopathy is continuing to theorize as to how bypass possibly works. The celecrated American 2-volume *Harrison's Principle of Internal Medicine,* from the 10th edotopm (1983) onwards through the latest 13th edition (1994), maintain the same refrain as follows below.

The text[3] offers e possible ways in which the bypass presumable works:

(a) Placebo effect. No wonder, bypass is often seen as the costliest aspirin.
(b) Sensory neurectomy: the bypass operation necessitates cutting the pericardial sac covering the heart, and thus sectioning the nerves mediating cardiac pain. Hence bypass may leave the coronaries unchanged but the patient no longer feels the pain, hence does not dread it to build up an alarm reaction, and thus feels well. No wonder, bypass yields no good results in asymptomatic persons.
(c) The reader should hold the breath, for "the pain may also have been alleviated as a result of infarction of the ischemic segment." Translated into ordinary English, it means bypass works by killing the complaining part of the heart. This is reminiscent of the Vietnam Was technique of scorching a village for the good of the occupant.

The confusion-worse-confounded over the modern miracles of angioplasty, bypass and the like may be cleared if one bears in mind: You can not do good by doing evil. Neither angioplasty nor bypass mollycoddles the coronary vessels. Plasty is a gross tearing of all the arterial coats. Bypass surgery – for every bypass – inflicts two $360^0$ wounds on the vascular bed, with the sutures exacting their own toll in terms of serving as nidus for atherosclerosis.

Some sea-change in medical thinking is due. Is it possible that coronary occlusion is not the culprit for heart attack?

It it possible that plasty and bypass, with the best of intentions, have been counterproductive? Could it tantamount to "friendly fire:? "the sense of *friendly fire* had been used in the Vietnam Was but was brought to prominence in the Gulf Was of 1991 when the majority of fatal casualties among allied troops were attributed to it."

Can an attempt be made to reread the nature of blood vessels and their relationship to the needs of the tissues they supply? The next section on TRAS Principles makes an attempt.

**TRAS Principle: Tissue Requisitions (its) Arterial Supply (I) Tissue Relinquishes (its) Arterial Supply (II)**

1. Arteries, Veins and Capillaries – the whole vascular tree – in aggregate length measure over 60,000 miles in an average human adult. As a tissue, it is universally spread in the body from scalp to sole. Medical science sees the heart as a large, muscularized blood vessel. An artery literally carries a person's heartthrob to each of the 1000,000 billion cells that make a human being. Capillaries and veins join arteries to complete a communicative network that carries gases, nutrients, hormones, antibodies, and so on to and fro.
2. From womb to tomb, and artery (with its capillaries and veins) does not exist by itself, but always in relationship to a tissue that it perfuses. The size of an artery, and its lumen, and the blood that it carries is always at the behest of the tissue supplied, and commensurate with the tissue's demand.
3. A human embryo, (representing all the vertebrates), taking cues from the needs of the various developing tissues, executes FOUR BYPASSES – between (a) the two atrial chambers, (b) the ventricular chambers, (c) the pulmonary artery and the aorta, and (d) the left umbilical artery and the inferior vena cava. Bypasses (c) and (d) are "major" arterial and venous channels respectively. The functional aim of all 4 bypasses is to circumvent the fetal lungs and the liver whose function is performed by the maternal placenta. The aforesaid bypasses illustrate on cardinal biologic principle: Functional necessity is the mother of structural innovation.
4. Dramatic changes occur in the circulatory system at birth: the transition from fetal dependence on maternal support via the placenta to the relatively independent existence of the infant in the outside world at birth brings about dramatic changes in the pattern of blood circulation within the newborn."[5] Within the first hour after birth to 3 months thereafter, all the above bypasses close down completely.

   The moral of the above dramatic events it that
   (i) The body knows when and how to create its own bypasses and to switch them off, and
   (ii) The clamping-shut of an artery (ductus arteriosus) is not alien to the body's working.
5. In adult life, there are some instances that convincingly illustrate the TRAS principles.
   (a) The *uterine* artery supplying a non-pregnant uterus, is quite small. On occurrence of pregnancy, the artery starts enlarging keeping pace with the demand of the uterus and the placenta. It is literally a change from a trickle to a torrent. On delivery of the baby, there occurs a process of involution whereby the uterus returns to its original size and so does the *uterine* artery.
   (b) A major step in the surgery of Coronary Artery Bypass Graft (CABG) is splitting the patient's chest in front midline involving a complete splitting of the sternum (chest bone). The operation ends by the surgical closure of the chest wound by stitches. Within few minutes after the closure, Nature sets itself to work. From nowhere cells sprout and turn into a billion capillaries that see to it that the whole wound is turned into a firm scar whenafter, without any ceremony, the capillaries disappear into nowhere.

(c) The removal of a tumour (benign or malignant) or any organ (tonsil, uterus, gallbladder) is invariably followed by the shriveling of the supplying artery, illustrating the principle that it was the presence and the demands of the tissues that had kept the artery patent.

6. A Biblical relationship binds a tissue to its arterial supply:
   *"Ask and it shall be given.*
   *Ask no more, and it shall be withdrawn."*
   An artery opens up if the tissue demands. Equally, an artery closes up if the tissue so dictates. The flow to the tissue is at the tissue's behest, the artery playing a faithful second fiddle all the time.
7. "It is suspected that thrombi in coronary arteries are more often the *consequence* of myocardial necrosis and severely depressed cardiac output than the *cause* of infarction."[6] Vermani[2], delivering an oration at the KEM Hospital opined that the above is a more likely sequence of events.

Coronary or carotid occlusion or narrowing is the *result* of altered demand from the heart or the brain and not the other way around. Hence all attempts at revascularization, no matter *what* the sophistry, end in no-again, no-win situation, for one can gain nothing out of treating an effect.
It has got to be accepted almost as polar reversal to current thinking, that the heart and/or the brain and/or the kidneys can pose no exception to the TRAS principle. Each of the tissues is given what it desires. Anything foisted on it, with the best of intentions, proves useless, or even counterproductive.

Coronary artery revascularization dates back from 1899 and thus be completing a 100 years shortly[7]. A 100 years of bypasses and plasties has not freed modern medicine from its honest submission that all that may be working is placebo and/or sensory denervation and/or killing of the complaining segment. The rallying cry against the irrationality of bypass or angioplasty is the demand that its benefit cannot and should not be claimed until double-blind controlled trials have revealed the same unequivocally.
Do not pray.
God is just.
**Christopher Marlowe**

Do not fret over the vascular supply to tissues; the arteries are just. Do what you like, the subtle *symphony between tissue demand and arterial response* will determine the outcome. To that extent, in all non-traumatic, age-related diminution in arterial supply to various tissues, the mechanical therapist is redundant.

Boyadjian[8], the Belgian cardiologist, in his monograph titled *The Heart* has generalized: "The technique of this by-passing is simple….. Nevertheless, we must insist on the following point: this operation does not cure the disease, but suppresses its principal symptom, which is anginal pain….. for, in spite of all the progress we have made, it is impossible to indicate with certainty the length of the expectation of life of patients suffering from coronary artery disease, and nothing up to now proves that a by-passing really increases that expectation".

If one were to bear in mind the TRAS principles, all our surprise at the lofty nonchalance with which the heart or the brain greets revascularization efforts would melt into nothingness. We would learn to respect what Walter Brandon Cannon, the famed American Physiologist called, in his book so titled – *The wisdom of the Body.*

Recently, the JAMA[9] published a *Centennial Series* of "51 Landmark Articles in Medicine" amongst which is the 1912 article by Herrick[10] on coronary occlusion and a 1983 postscript on it by the redoubtable Hurst[11] that reads rather tellingly: "A debate still exists as to whether coronary thrombosis is the cause or the result of infarction and whether it is always present in myocardial infarction. The debate as to the frequency of thrombosis identified at angiography and the frequency of thrombosis found at autopsy in patients with myocardial infarction is an important one and is not settled." The fact that phenomenon called *reperfusion injury* is clearly accepted[3] to exist – in carotid field as well – puts paid to the *idee 'fixe'* of restoration of coronary lumen as *the summum bonum* of invasive cardiology. TRAS Principles at least hint at the possibility that Dean Ornish[12] need not strive to *reverse* CAD, for it may not really be the problem in the first place.

In the whole CAD game, the coronaries are treated as the driver can cordium as the driven. A point that has been missed is that in the car called CAD, coronary could as well be the chauffeur driving under backseat orders from cordium the owner.

One can describe the current medical scene as greatly dominated by coronary ReRheologists whose chief reputation resides in the number of surgeries and their mega-gees. Ardrey[13] the anthropologist, had elaborated upon "the disastrous consequences of applying utter logic to a false premise." The unimaginably sophisticated coronaryologists might retort that what they practice is science. – "What d'you think science is - a magic wand that you just have to wave to get what you want?" having posed a question, Solzhenitsyn[14] questions further: "Supposing the problem's been put in the wrong terms or new factors crop up?" The problem-put-wrong is the coronaryological assumption that coronary-blockade is THE culprit. And the new factors that crop up are related to our rurning a Nelson's eye to the naïve assumption that *good* can be procured for the heart by perpetrating *evil* on the coronaries.

We conclude this maverick presentation with a prophesy that the biology of coronary/carotid fields appears to be in no mood to oblige the ReRheologists who must sooner or later phase out into an inevitable therapeutic oblivion. The TRAS principles One and Two are an intellectual attempts at fathoming the inscrutable face of what is called CAD, and its invasive management, wherein C stands not only for coronary but carotid as well.

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