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In memoriam

These Lecture Notes are dedicated to the memory of Dr. Erwin Van den Enden, who passed away unexpectedly on May 5, 2013. The Illustrated Lecture Notes are Dr. Van den Enden's magnum opus. They form an invaluable body of reference for both students and practitioners of tropical medicine. Dr. Van den Enden spent decades on this project, expanding on the knowledge of his predecessors at the Institute of Tropical Medicine. His colleague and mentor, Dr. Jef Van den Ende, explains how Erwin enriched his life:

On May 5, 2013, our colleague Erwin Van den Enden was unexpectedly taken from us. Dr. Van den Enden was a corner stone and buttress of the Medical Services of the Institute of Tropical Medicine, Antwerp.

Dr. Van den Enden preparing a vaccine vial at Marymount Mission Hospital, Zimbabwe, 1981

First and foremost, he was a homo doctus. He could engage in more than knowledgeable conversation about the Higgs particle, butterflies, crystals or even the Hubble telescope and distant galaxies. He pointed out to me one day that a medical doctor should read the 'Scientific American' too, to be truly deserving of the title "Doctor". I subscribed the same day.

As homo universalis he was a bicyclist and invested an enormous amount of time in raising his two sons and being a caring husband. He went on missions to Africa under dreadful conditions and took me by surprise once by – out of the blue – playing two magnificent pieces

of jazz on my piano.

Above all we will remember him as a clinician and professor. He could thoroughly analyze clinical cases, study the publications and lead the team on a journey through biochemistry, physiopathology, pathology and the history of medicine, all based on one case.

As professor (he unfortunately never obtained the title because of a shift in focus from education to research at the end of the 20th century in most universities), he was unparalleled. He was a guest teacher in Amsterdam, at John Hopkins, in Lima and elsewhere, and could completely enthrall students with his lectures about tropical spiders and snakes – even those suffering from a serious hangover from the previous night.

Dr. Van den Enden preparing a vaccine vial at Marymount Mission Hospital, Zimbabwe, 1981

“They don’t make these kinds of people anymore,” a student once said about him. Duly noted.
Jef Van den Ende, ITM.

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A tropical disease tour

Tribute to Dr Erwin Van Den Enden

We would like to give Dr. Van den Enden the word for the Introduction (written in 2013), which remains an extraordinarily accurate and modern diagnosis of the current global situation.

“We are taking a panoramic tour through a number of medical subjects. An attempt has been made to provide a picture of a number of problems. Hopefully this has whetted the reader’s appetite and he/she will be motivated to continue to learn and contribute to the ever-increasing knowledge and use this for commendable purposes. We hope this course will be highly interactive, and not lead to “death by power-point” in the class room.

Many rural areas in the tropics seem to be frozen in time (although cell phone use spreads fast), while the flow of medical and scientific information has become a deluge. Getting information resembles trying to drink from the water of a fire hose. We are living in the middle of several revolutions, from explosive expansion of genetic and biomedical data, to fundamental changes in information / communication strategies. Rapid advances in robotic surgery, rapid diagnostic tests, the promise of stem cell therapy, the approval of the first gene therapy in 2012 (Glyvera), brainbow cell staining, fast internet access, attosecond lasers, quick gene cloning, optogenetics, metagenomics and transgenic organisms suggest that we enter a world with surprising new possibilities and risks. There is so much new information available that we are in danger of becoming overwhelmed by it, so choosing what to study becomes more and more important. Maybe a part of the style of learning is changing right under our noses as well. With lots of information coming in small “Mc”-bite size portions, there is a danger of losing an overview or a proper reference frame. With electronic data overload, certain students might have a diminishing ability to stay focused on a single item for a prolonged and reasonable time. We have to get a firm broad and constant education, based on factual knowledge and mastering applications, together with empathy as

well as fluency in divergent and convergent thinking. I think it is a good idea that a physician can talk with a marine biologist, a geochemist and an entomologist and of course the patient. Drawing hard dividing lines between academic disciplines makes it more difficult for researchers to communicate and cooperate.

Other items on a very different level -to name just a few- are the looming freshwater crisis in certain geographical areas, the dramatic increase of the world population, the “population greying” in several countries and loss of habitat, biodiversity and the near-exhaustion of unique natural non-renewable resources such as geological phosphate deposits.

The unrelenting spread of multiresistant pathogens is becoming a global emergency and will become one of the most serious infectious disease problems facing the world in the near future. The spectrum ranges from multidrug-resistant malaria, *Staphylococcus aureus*, tuberculosis, ceftriaxone-resistant gonorrhea, carbapenem-resistant Enterobacteriaceae to triclabendazole-resistant *Fasciola hepatica*. Treatment of bacterial infections with bacteriophages is still experimental at this moment.

Another threat is the possibility of a new pandemic of a highly contagious and lethal disease, be it a new influenza, a SARS-like pathogen or something nobody expected.

In this course, the emphasis is on tropical medicine. Let’s try to get the outlines right, getting a good grip on basic principles as currently understood, before diving deep. It is true that a jack-of-all-trades is usually a master of none. So be it, but it eases communication between disciplines. A study of the details comes afterwards (since we’ll all be life-long learners) and often shows how rich nature is if we only want to see. Admiration of nature goes best together with understanding of nature. Understanding the structure of a flower does not diminish the beauty of a rose. Hence the following by William Blake”.

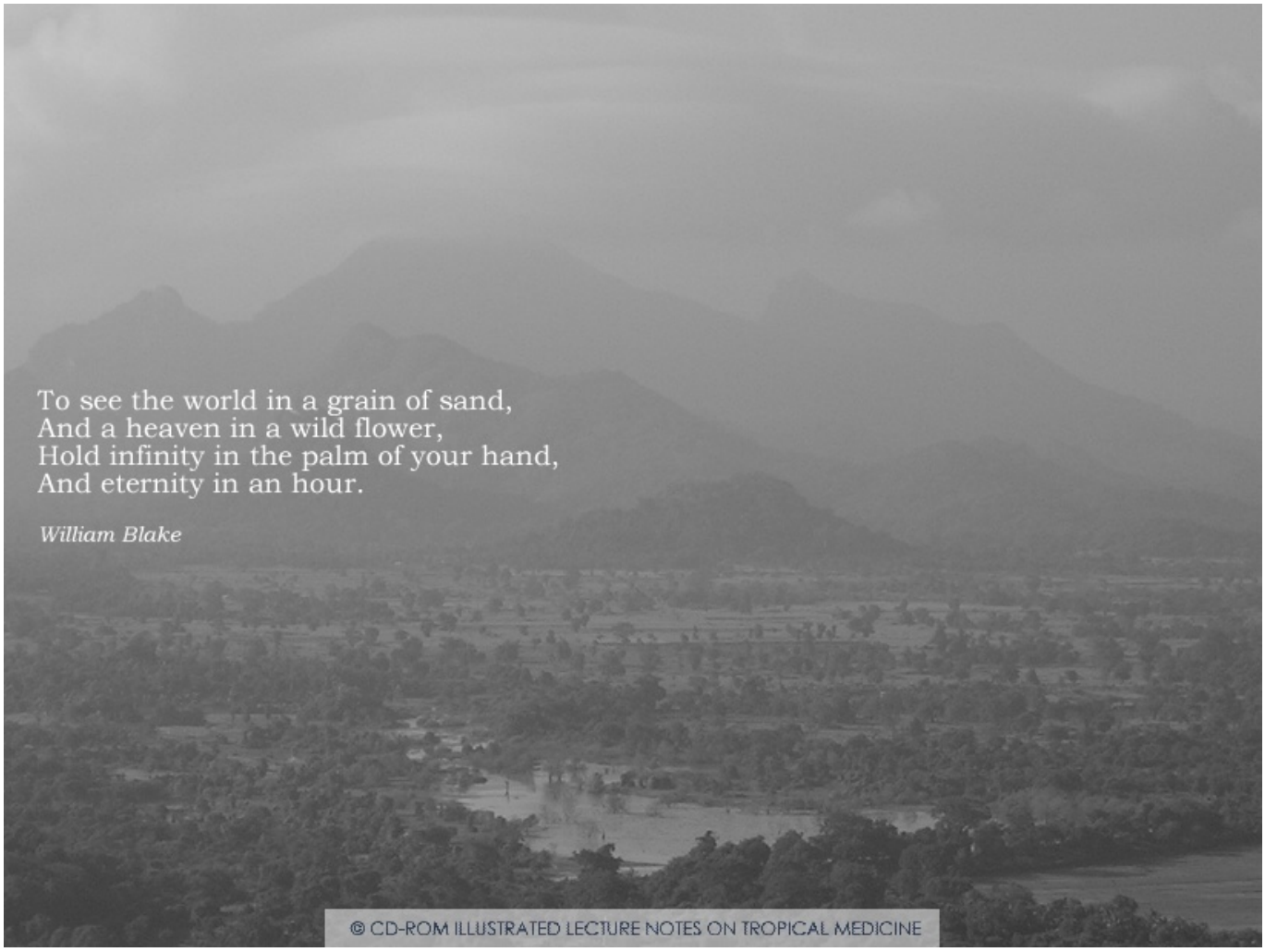

Photo courtesy of Mr Jan Van den Enden

Van den Enden Erwin, MD
Antwerp, Belgium
April 2013

Navigation guide

"To wrest from nature the secrets which have perplexed philosophers in all ages, to track to their sources the causes of disease, to correlate the vast stores of knowledge, that they may be quickly available for the prevention and cure of disease – these are our ambitions".
Sir William Osler.

The great majority of diseases in tropical regions are cosmopolitan which means they are found throughout the world: pneumonia, burns, fractures, diarrhoea, asthma, diabetes, hypertension and schizophrenia. Some disorders were also previously found in Europe, but here they have largely disappeared: leprosy, vivax malaria, plague. Only a few diseases occur exclusively in tropical regions, e.g. African sleeping sickness. A number of diseases have disappeared in the West as a result of the improvement of living conditions. The classic, predominantly parasitic tropical diseases are for the most part not the main cause of disease in developing regions, except in certain localized areas where there is a high prevalence. The main medical problems in Third World countries at present continue to be respiratory tract infections, diarrhoea, tuberculosis, malaria, AIDS, measles, accidents, anaemia and pregnancy-related problems. Hepatitis B and C, pelvic inflammatory disease and epidemic meningococcal meningitis are also frequent problems.

As economies develop, other diseases previously first seen in Western countries will become more common, such as cancer, dental caries, cardiovascular diseases and multiresistant micro-organisms. Problems typical of large cities will become more important in the near future as urbanization increases in less developed countries. The poor neighbourhoods and slums of conurbations such as Cairo, Lagos and Kinshasa in Africa, Sao Paulo, Rio, Lima and Bogota in South America, Dhaka, Calcutta, Bombay, Delhi, Karachi and Manila in Asia pose their own problems, but also offer opportunities for improvement.

Some concepts recur constantly in these lecture notes and are explained below.

Parasite: a parasite is an organism that lives in or on another organism and draws its nourishment from it (from the Greek “para-sitos”: beside food). Strictly speaking, it has no connotation of harmfulness or otherwise. Usually, however, the meaning is taken in a narrower sense and the term is used to refer to various worms, protista and arthropods which have another organism as their habitat. Parasites often have a complicated life-cycle with well-defined hosts and a specific mode of transmission.

Protista: unicellular organisms that contain a cell nucleus surrounded by a nuclear membrane: eukaryotes (as opposed to prokaryotes – bacteria). There are specific treatments for each disease.

e.g. Sleeping sickness, malaria, amoebiasis, leishmaniasis, giardiasis, toxoplasmosis.

Metazoa: multicellular eukaryotic organisms, diverging considerably in size and taxonomic relationship. E.g. whip worms, schistosomiasis, scabies, lung flukes.

Paratenic host: a host in which a parasite lives and survives, but does not develop further.

Vector: an intermediate host, which transports a parasite from the previous host to the subsequent one. E.g.: the tsetse fly is the vector of African sleeping sickness.

Arthropod: invertebrate animal with articulated legs. In medical practice the main arthropods belong to the group of insects and arachnids (including ticks and mites). Copepods are also arthropods and are vectors for a number of organisms.

Epidemic: infection which fairly suddenly affects a large number of people at the same time. E.g. the plague epidemics in the Middle Ages in Europe, the meningitis epidemics in the Sahel.

Pandemic: epidemic which spreads around the whole world. E.g.: Flu (influenza), AIDS pandemic

Endemic: a disease is endemic if it is chronically present in a particular region. E.g.: in Africa there are foci of endemic malaria.

Transmission: transport of an organism can occur in various ways.

Mechanical transmission, comparable to sharing a dirty needle. This can occur in rapid repetitive blood meals of mobile insects on different hosts, e.g. the host reacts to the pain caused by the bite and interrupts the insect’s feeding. The hungry insect will soon try to bite a second host and infect him via the blood of the first host which is still sticking to its mouthparts. This sort of transmission, however, is rare, e.g. tularemia spread by tabanid flies.

Biological transmission, in which the pathogenic organism either (1) reproduces in the vector (e.g. plague, arboviruses), (2) undergoes maturation before it becomes infectious (e.g.

river blindness), (3) both reproduces and undergoes maturation (e.g. malaria, sleeping sickness).

Taxonomy, nomenclature and the concept of species

In 1758 Linnaeus published the tenth edition of "*Systema naturae*", in which he used the binomial system consistently, also for animals. This work represented a turning point in zoological terminology. It is due to his work that we have a naming system with two parts: first the genus and then the species. E.g. *Schistosoma mansoni*, *Escherichia coli*, *Aedes aegypti*. If there are subspecies (races), a third word is added, e.g. *Trypanosoma brucei gambiense*. Thus, living organisms are divided into hierarchical groups according to the similarities in their structure. The successive groups are: Kingdom, Phylum, Class, Order, Family, Genus and Species. A mnemonic sentence to help to remember the sequence is "**K**ing **P**hillip **C**ame **O**ver **F**or **G**ood **S**paghetti".

Sometimes a subgenus is given and is written between brackets, e.g. *Aedes (Stegomyia) aegypti*. When there are species complexes, as in *Simulium damnosum*, reference is often made to *S. damnosum* s.l. (sensu lato – in the broad sense, i.e. the species complex) or *S. damnosum* s.s. (sensu stricto – in the narrow sense). Different groups within a complex may exhibit very different patterns of behaviour. Thus, *Anopheles gambiae* sensu strictu is highly anthrophilic, while the sister species *Anopheles quadriannulatus* is totally zoophilic and has no medical significance. The presence of the latter in an environment, however, can cause confusion in a control programme.

Example: Order: Diptera

Suborder: Nematocera

Infra-order: Culicomorpha

Superfamily: Chironomoidea

Family: Simuliidae

Subfamily: Simuliinae

Tribe: Simuliini

Genus: *Simulium*

Subgenus: *Erwardsellum*

Species: *Simulium (Edwardsellum) damnosum*

According to the “International Code of Zoological Nomenclature”, the genus name is always written with a capital letter and the species name always with a lower case letter (e.g. *Glossina tachynoides*). This applies even if the name is derived from a proper name, e.g. *Culicoides grahamii*. In scientific publications, genus and species name are italicised or underlined. Names also never contain an accent, apostrophe or umlaut (thus no *Aëdes aegypti* or *Tipula o’neili*). Two words are sufficient, e.g. *Mycena luxaeterna* for a luminescent mushroom species (instead of *Mycena lux aeterna*). The name of the genus can be abbreviated, e.g. *Anopheles funestus* becomes *A. funestus* if this does not lead to confusion or potential mistakes in the text. Sometimes the generic name is abbreviated to two letters to prevent confusion. Suppose a text contains the mention of *Culiseta* and *Culex.* If both are abbreviated to *C*. then it is no longer possible to know to which this refers. If *Culex* is identified by *Cx*. then clarity is restored. Sometimes the name or the initials of the discoverer of the species are included (not italicised), possibly with the year of description: e.g. *Enterobius vermicularis* (Linnaeus, 1758). This mention of the name, however, is optional and does not form any part of the actual scientific name. In view of the fact that knowledge and opinion are constantly changing, taxonomic classifications (certainly the “middle groups”) sometimes differ from author to author and according to the time of publication. There is no such thing as “The One Final Correct Classification”.

Conventionally, the species is defined as a population which can reproduce among itself and which is reproductively isolated from other populations. This appears clear when we talk for example of humans, horses, wild ducks or rattlesnakes, but with other organisms it is much less obvious. What is the situation with the taxonomy of extinct species? What about symbiotic organisms, from lichen to protista, which cannot live without their symbiont? Some

organisms have no sexual reproduction (for example amoebae). If there are sterile hybrids (e.g. horse x donkey-> mule), then this is an answer. Sometimes however there are fertile hybrids (some animals, many plants). The problem of species definition is central in biology at present. This has practical implications for example for the better understanding of the variability of diseases such as amoebiasis, leishmaniasis or Chagas' disease. Better insights into vector populations also depend on good definitions (some morphologically identical mosquitoes appear genetically to consist of various complexes with, for example, differing biting or reproductive behaviour).

Diagnosis

There are various ways of reaching a diagnosis. The saying: "One recognizes only what one knows" is of great importance. Knowledge of diseases and pattern recognition are the basis. Recognition of clinical presentations and reaching a diagnosis is the outcome. In the case of infectious diseases, an attempt can be made to detect the pathogenic organisms directly by microscopy (for example thick smear for malaria, Ziehl-Neelsen staining of sputum for pulmonary tuberculosis, fecal specimen for amoebae, bone marrow aspirate for visceral leishmaniasis, etc.). Cultures and serological tests are usually difficult or impossible in rural areas. Radiology and ultrasound are mostly of limited availability.

A patient will have certain complaints: symptoms, examples of which are neck pain, cough or loss of strength in the legs. There will also usually be objective signs identified by the physician treating the patient. Examples are neck stiffness, crepitations and hyperreflexia. One and the same disease may take different forms in different people. There is a spectrum of manifestations: there is individual variability (for example immunological resistance) and furthermore the symptoms and signs depend on the stage of the disease. Sometimes the degree of infection (for example worm load) is important. Whether a particular symptom, for example blood in the urine (hematuria), is highly indicative of a specific diagnosis depends on the local frequency (prevalence) of the disorder (for example, bilharziasis is frequent in Africa but not in India). A symptom may be specific to a greater or lesser extent, for example fever can be caused by numerous diseases. Fever is thus fairly unspecific on its own. On the other hand, muscle spasms triggered by sudden noise are strongly indicative of tetanus. This sign rarely occurs in other diseases and is thus relatively specific for tetanus.

Often, a definite diagnosis is not possible and a probable diagnosis must be established: the disease that is most likely in the differential diagnosis. The differential diagnosis is the list of those diseases that might explain the patient's clinical picture. It is not advisable to make a long list by including all sorts of rare possibilities. By definition, rare diseases are always rare. It is however important to think of a rare disease if it is severe and treatable in the given circumstances.

Treatment

Priorities play a major role. For example: with a limited budget, a renal dialysis unit will not be built at the expense of everything else. "What is the importance for this patient?" must be asked, but: "What is the importance for public health?" should also be considered. In the choice of medications, cost price and availability are also of importance. The WHO has compiled a list of essential medicines.

Since the discovery of penicillin in 1928 and it's production in 1938 and Prontosil and related sulfa drugs after 1932, antibiotic resistance has been on the rise. This is currently threatening many gains in infectious diseases which have been made over all those decades. The first penicillin-resistant bacteria where already identified before penicillin came on the market in the 1940s, methicillin-resistance was documented in the 1980s and vancomycin-resistance in the 1990s. It is estimated that more than 50% of the world production of antibiotics is for use in the agricultural sector, not to cure sick animals by veterinarians, but for food additives. New threats include multi-resistance in a multitude of pathogens including *Plasmodium falciparum, Mycobacterium tuberculosis*, methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant enterococci and the appearance of *Klebsiella pneumoniae* carbapenemase (KPC) and New Delhi metallo-beta-lactamase (NDM-1) in several Gram-negatives in the first decade of the 21st Century. Since (1) Gram-negative bacteria easily share resistance genes across species, (2) fewer new antibiotics are discovered due to several reasons, (3) and the increase in world travel -both numbers of people and speed of travel-, the conditions for a perfect storm ("total resistance") are in the making, threatening to bring us back to conditions similar to where we were during World War One. The bottom line in pharmaceutical industries is financial gain. The development of new classes of drugs to treat multi-resistant bacteria is rather challenging. Even if successful, the

drugs will probably be used for a short period of time before resistance arrives, and therefore are not considered to be worth the great expense of research and development time. Better incentives (e.g. longer patent protection) are needed. Maybe formal agreements such as were used during polio vaccine development are needed to protect companies against financial disaster. Basic as well as applied research needs to be boosted. Let's hope that we won't need a Manhattan-type of project if things seriously get out of hand. In our direct workplaces as doctors and nurses, meticulous disinfection of hands and surfaces will need to be instituted to limit spread and outbreaks.

Prevention

Prevention is better than cure. Sometimes prevention is the only feasible measure (for example HIV).

Prevention is based on:

- Vaccination: for example measles, polio, diphtheria, tetanus, whooping cough, yellow fever
- Chemoprophylaxis: for example the regular intake of antimalaria tablets
- Interruption of transmission. A good knowledge of the biological cycle of the pathogen is necessary for this. For example, control of the tsetse fly for sleeping sickness. Interruption of epidemic typhus transmission by delousing.
- Information, health education and encouragement of personal hygiene e.g. via school.
- Genetic counselling has its place in a number of hereditary diseases.
- Clean drinking water and food, use of good sanitary facilities. Quality control of food and drinking water is essential if it can be coupled to action to improve the situation.
- Food supplements: e.g. vitamin A, iodine deficiency
- Rapid isolation and treatment of infectious diseases (e.g. Ebola fever, open pulmonary tuberculosis, plague).
- Epidemiological surveillance (regional, national, international) is important.
- Combating poverty is the best prevention

Disclaimer

This book is not intended to be a comprehensive review of Tropical Medicine. Instead, it aims to provide an overview, highlighting the diverse and intriguing diseases predominantly found in tropical regions. We hope to spark further interest on this topic that we love.

To note, we purposely did not include Tuberculosis and HIV chapters, due to the fast changing nature of them and availability of high quality quidelines.

Useful manuals: Tropical medicine

- Medical practice in developing countries by Krawinkel (ISBN 3-8243-1276-X).
- Médecine tropicale by Gentilini & Duflo.
- Manson's Tropical Diseases by Cook and Zumla (published by Saunders, 24th edition 2023).
- Tropical Medicine and Parasitology by Goldsmith (published by Prentice-Hall International).
- Care of the critically ill patient in the tropics and subtropics by Watters (published by McMillan).
- 100 Clinical Problems in Tropical Medicine by Harries (published by Baillière Tindall).
- Common Medical Problems in the Tropics. Ed: Schull. MacMillan Publishers. ISBN 0.333.67.999.7
- Lecture notes on Tropical medicine by Bell (published by Blackwell Science).
- Online clinical cases Gorgas course (Peru): http://www.uab.edu/medicine/gorgas/cases-blog
- Online tropical radiology: http://www.isradiology.org/tropical_deseases/tmcr/main.htm
- Online mycology: http://www.mycology.adelaide.edu.au/Mycoses/
- Online medical algorithms (requires free log-in): http://www.medal.org/Visitor/login.aspx
- Kabisa: Interactive training program for clinical practice in tropical and subtropical available on this website.

Reflections

Medicine is far from static. The work facing clinicians in the tropics mainly consists of cosmopolitan problems. The classic tropical diseases will probably become less important,

while obesity, hypertension, heart disease are increasing in low-resource settings and a massive diabetes epidemic is unfolding. A tsunami of new data threatens to overwhelm scientists, although creative use of networked silicon chips helps.
In medicine, we would like not only to form highly qualified professionals, but also balanced caring people with a gentle touch and a spark in their eyes. The illustrations and case studies discussed during the actual teaching course will help to identify the important points.
Sometimes, after all the studying, it is nice to let your mind drift and reflect on the big picture and dream your dream(s). The following has nothing to do with tropical medicine, but I would like to include here one of my favorite poems, just because I think it is beautiful. It was written by Max Ehrmann in 1927.

"Go placidly amid the noise and the haste, and remember
what peace there may be in silence.

As far as possible, without surrender, be on good terms with all persons.
Speak your truth quietly and clearly; and listen to the dull and ignorant;
they too have their story.

Avoid loud and aggressive persons; they are vexations to the spirit.
If you compare yourself with others, you may become vain or bitter,
for always there will be greater and lesser persons than yourself.

Enjoy your achievements as well as your plans.
Keep interested in your career, however humble;
it is a real possession in the changing fortunes of time.

Exercise caution in your business affairs, for the world is full of trickery.
But let this not blind you to what virtue there is;
many persons strive for high ideals and everywhere life is full of heroism.

Be yourself. Especially do not feign affection.
Neither be cynical about love; for in the face of all aridity and disenchantment,
it is as perennial as the grass.

Take kindly the counsel of the years, gracefully surrendering the things of youth.
Nurture strength of spirit to shield you in sudden misfortune.
But do not distress yourself with imaginings.
Many fears are born of fatigue and loneliness.

Beyond a wholesome discipline be gentle to yourself.
You are a child of the universe,
no less than the trees and the stars and you have a right to be here.
And whether or not it is clear to you, no doubt the universe is unfolding as it should.

Therefore, be at peace with God, whatever you conceive Him to be.
And whatever your labours and aspirations,
in the noisy confusion of life, keep peace with your soul.

With all its sham, drudgery and broken dreams, it is still a beautiful world.
Be cheerful. Strive to be happy."

Max Ehrmann, "Desiderata", 1927

Authors and collaborators

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