OXYGEN-OZONE THERAPY IN THE PREVENTION OF THE OXIDATIVE CELLULAR DAMAGE: AN ANTIAGEING HYPOTHESIS

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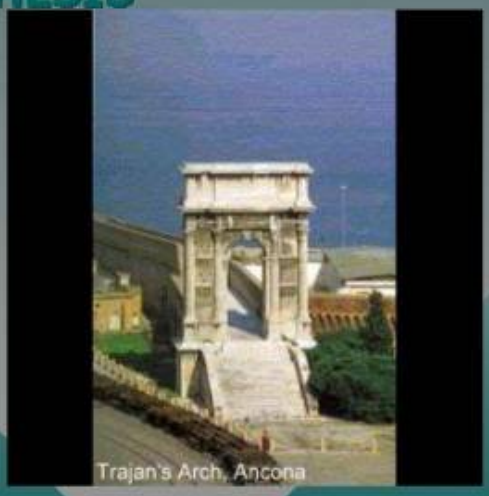

Trajan's Arch, Ancona

INTRODUCTION

Since many years the role of reactive oxygen species (**ROS**) in the acute and chronic diseases represented the topic of numerous scientific papers. Indeed, the oxidative damage to DNA, RNA, protein and cell membranes that physiologically occurs during the ageing process and the partial protection exerted by the cell defence systems represent well-known processes. On the other hand, in various pathological conditions the main problem is related to a rapid increase in the cellular **ROS** concentration that exceeds the capacity of the cell to eliminate them. Normally, **ROS** derived from the oxygen reduction during the biochemical pathways of the cell energy production systems (*Gershman, Science, 119: 623-626, 1954*). In some pathological conditions **ROS** could increase either for a primitive defect of the cell defence system or following an overproductions derived either from the cell death or apoptosis phenomena. Nevertheless, the role of the oxidative stress in the induction of apoptosis is well known and the oxidation of glutathione represents an early event in the course of apoptosis.

BIOCHEMISTRY OF AGEING

Age-related impairment in the respiratory enzymes not only decreases ATP synthesis but also enhances production of ROS through increased electron leakage in the respiratory chain . The mitochondria generate most of the cellular energy by oxidative phosphorylation and produce most of the toxic ROS as a by-product (***superoxide radical anion , hydrogen peroxide , hydroxyl radical***). Other source in ROS production is represented by phagocytosis processes. Moreover, the activity of the defence system against ROS decrease with age. They are mostly represented by Cu,Zn-SOD, catalase and glutathione peroxidase, whereas Mn-SOD activity increases with age up to 65 years and slightly declines thereafter in skin fibroblasts. Such an imbalance in the function of antioxidant enzymes may result in excess production of damaging ROS in the cell.

ANTIAGING DEFENCES

The natural defences against ROS could be classified as exogenous or endogenous.

The first ones, diet dependent, comprise

vitamins, E and C

flavonoids

polyphenols (mangiferin)

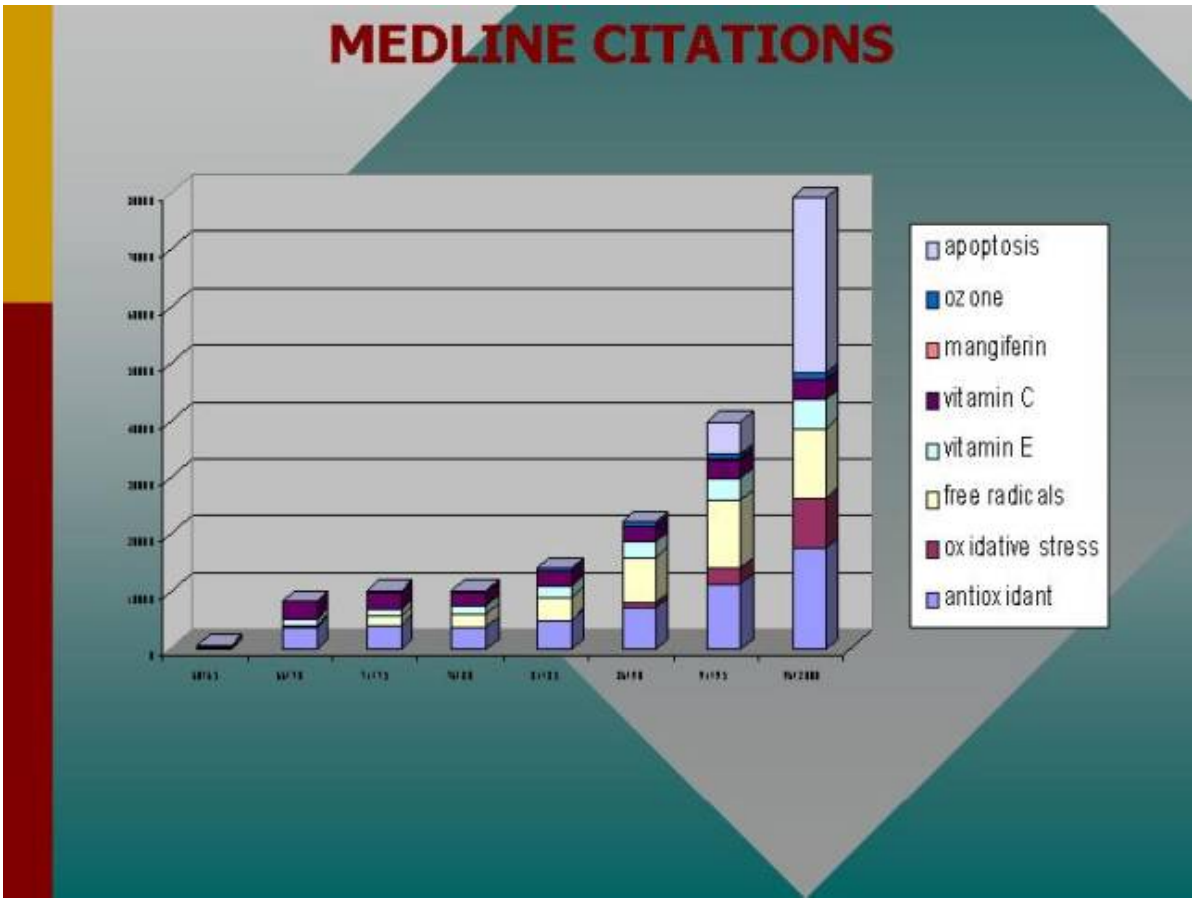
The endogenous, genetically determined, are

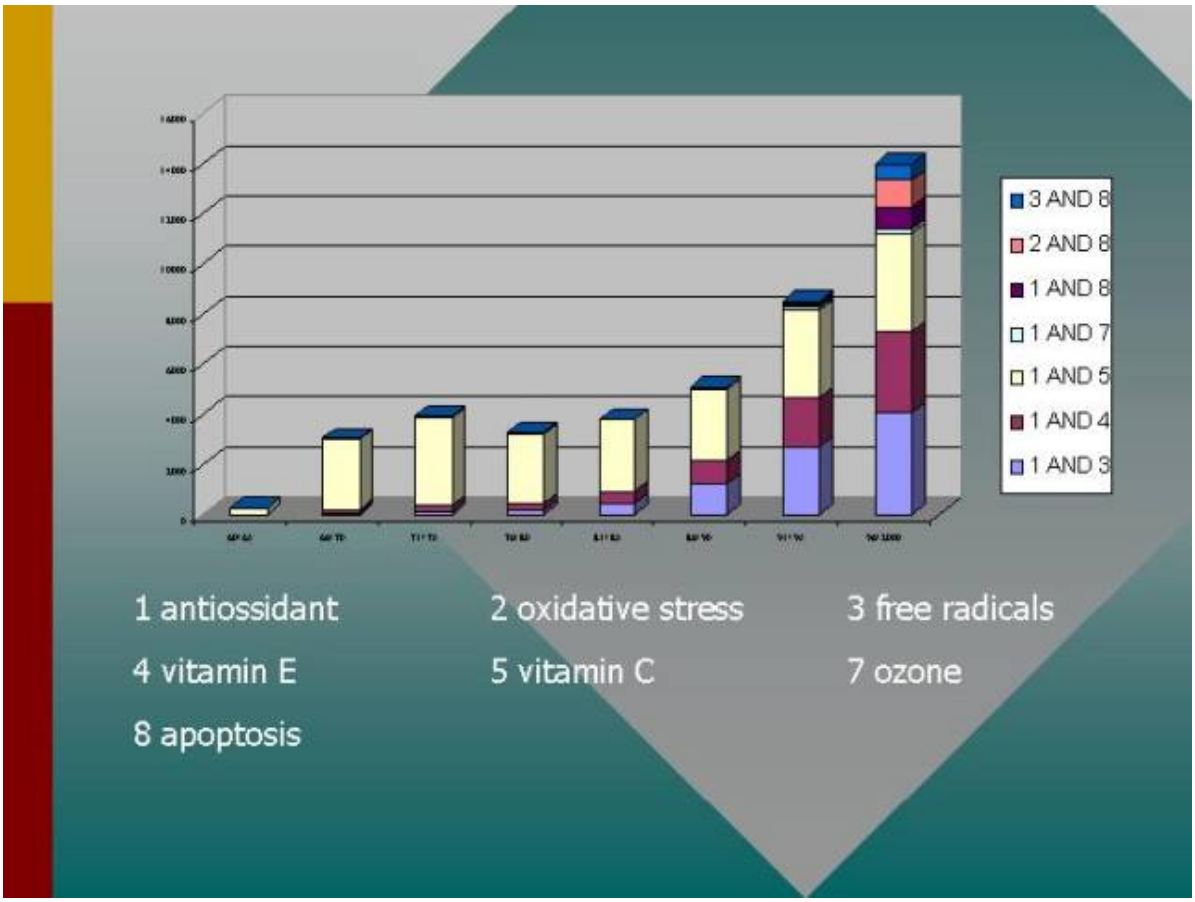
SOD

glutathione peroxidase

catalases

In the last group a key role is exerted by some enzyme cofactors such as Cu, Zn, Mn and Se.

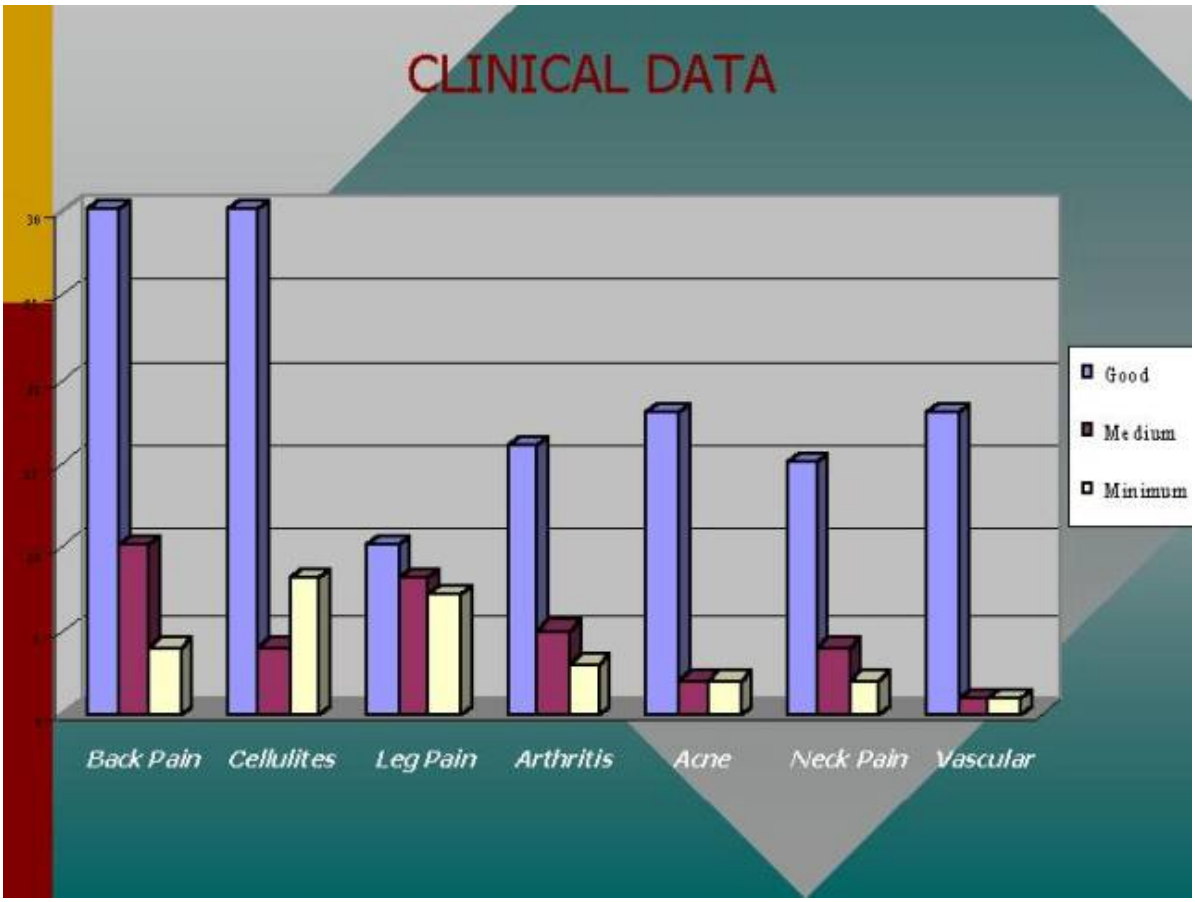

MEDLINE CITATIONS
apoptosis
ozone
mangiferin
vitamin C
vitamin E
free radicals
oxidative stress
antioxidant

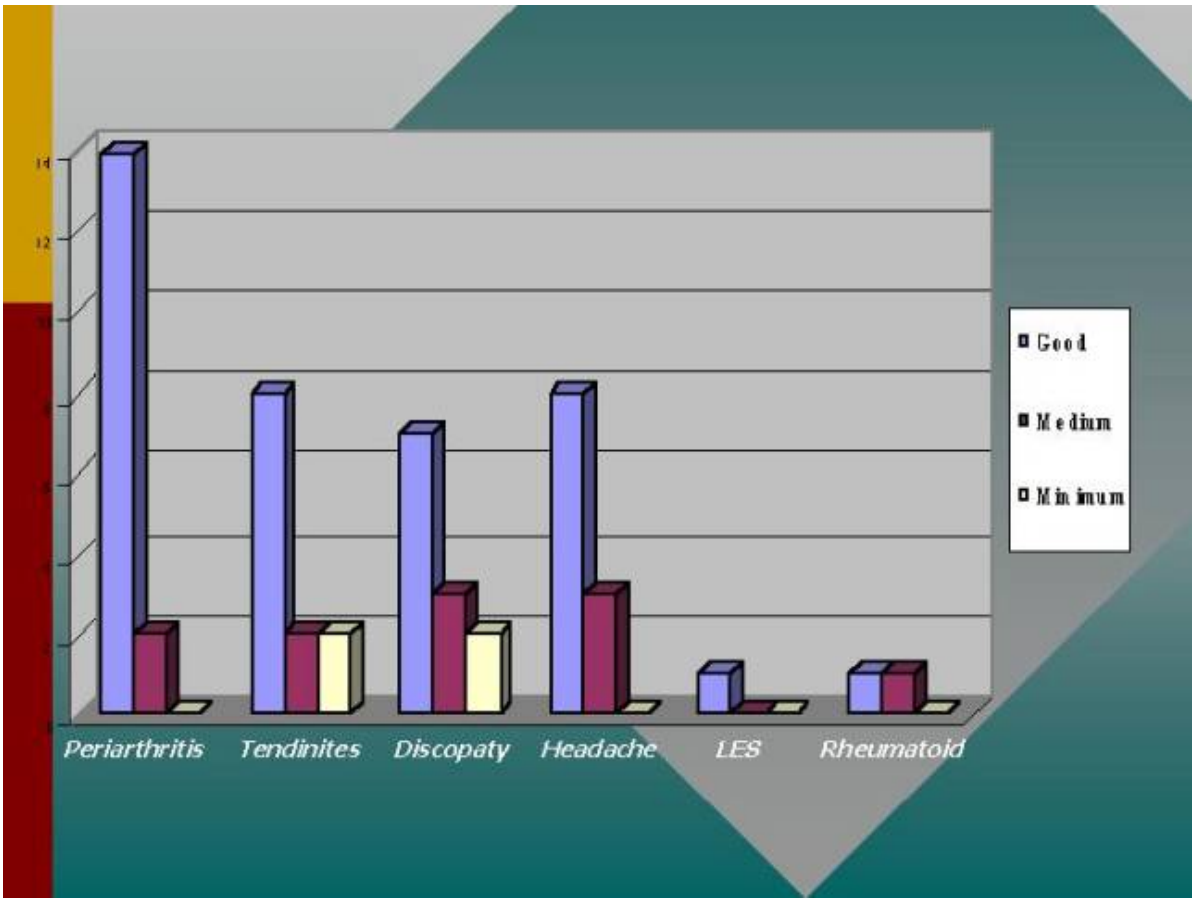

3 AND 8
2 AND 8
1 AND 8
1 AND 7
1 AND 5
1 AND 4
1 AND 3
1 antiossidant
2 oxidative stress
3 free radicals
4 vitamin E
5 vitamin C
7 ozone
8 apoptosis

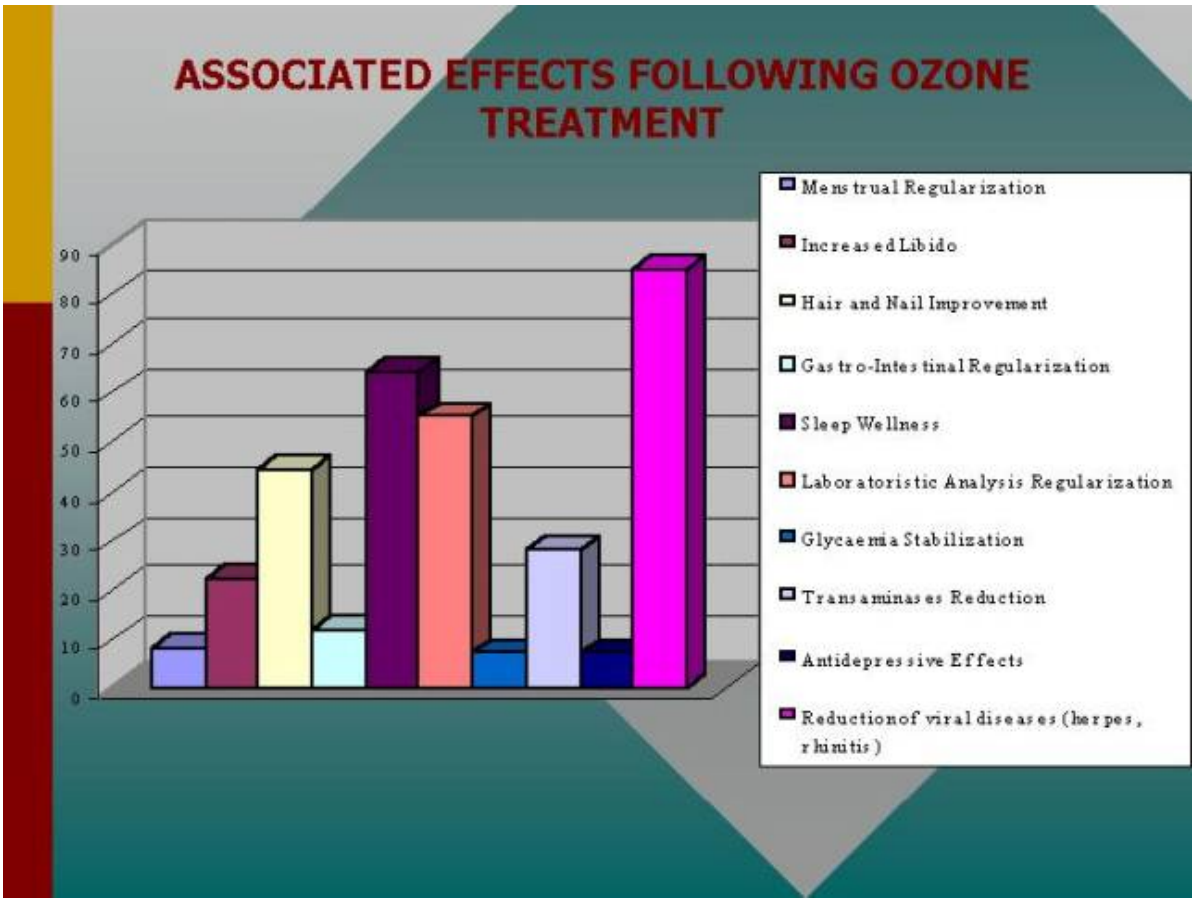
ANTIAGEING HYPOTHESIS AND EXPERIMENTAL MODELS

The first hypothesis of a positive conditioning induced by low ozone concentrations against the oxidative stress has been recently proposed by Leon Fernandez et al (Int. Cong. Pharmacol., CPT 2000, Florence, Brit J Clin Pharmaco, July 15-20, 2000). The theory is based upon the fact that low, non-toxic, ozone doses could raise the efficacy of the endogenous system by increasing the production or the activity of some antioxidant enzymes isoforms. Looking at the ischaemic preconditioning in which is scientifically proved that repetitive brief ischaemia plays an important role in the acquisition of late-phase cardio protection against ischaemia/reperfusion injury in rats (Yamashita et al, Br J Pharmacol, 131(3): 415-422, 2000), we can speculate that repetitive brief oxidative stress induced with low ozone doses could ameliorate the cell defences mechanisms against ***ROS****. The hypothesis is supported by other data reported by Rao and Shaha (Free Radic Biol Med, Nov 15; 29 (10): 1015-1027, 2000) demonstrating the formation of multiple isoforms of glutathione S-transferase after the exposure to H2O2.*

A further evidence of the protective action induced by low ozone concentrations has been proposed by our group (Re et al, Gen Pharmacol, 32; 245-250, 1999). Indeed, we proved the reduction of the intracellular calcium at presynaptic levels after the exposure to low ozone doses. The cytosolic calcium could be considered as the common final pathway of the cellular damage, either physiologically or pathologically. A low calcium level represents a further element in supporting the idea of the oxidative cell damage protection either in the chronic or in the acute ageing. We think that the use of ozone in the medical field could represents a useful and safety therapeutic potential in many pathologies actually orphan of adequate pharmacological treatment and in the prevention of the naturally occurring ageing.


CLINICAL DATA
Good
Medium
Minimum
Back Pain
Cellulites
Leg Pain
Arthritis
Acne
Neck Pain
Vascular


14
12
Good
Medium
Minimum
Periarthritis
Tendinites
Discopaty
Headache
LES
Rheumatoid


ASSOCIATED EFFECTS FOLLOWING OZONE TREATMENT
90
80
70
60
50
40
30
20
10
0
Menstrual Regularization
Increased Libido
Hair and Nail Improvement
Gastro-Intestinal Regularization
Sleep Wellness
Laboratoristic Analysis Regularization
Glycaemia Stabilization
Transaminases Reduction
Antidepressive Effects
Reductionof viral diseases (herpes, rhinitis)

COMMENTS AND CONCLUSIONS

In conclusion we think that in parallel with the well known ***oxygen paradox***, intended as the paradox of the life on the earth where oxygen is essential for the life being in the same time life limiting, we can introduce the ***ozone paradox***. Indeed, as oxidative agent by a pure chemistry point of view, could represent a valid tool in limiting the toxic damage when used as preconditioning agent at low concentration.

The scientific data indicate that the administration of low ozone concentrations (3-5 μg/ml) could represent a challenge in the ageing processes. Indeed, it has been clearly demonstrated its positive action during *acute* ROS iperproduction (pathological and traumatic conditions). Nevertheless, we think that it could be useful to prevent and defend from the *chronic*, natural occurring, ROS production in the ageing. The observed patient status during a period from 6 months to 3 years following the treatment showed an increasing wellbeing. More epidemiological studies are needed in the future but, we think, the ozone preconditioning must be considered as a main research topic for the future.

The Vaccination Theory a Surprising Similarity

•Edward Jenner and the Discovery of Vaccination

•The year 1996 marked the two hundredth anniversary of Edward Jenner's first experimental vaccination--that is, inoculation with the related cow-pox virus to build immunity against the deadly scourge of smallpox.

•Edward Jenner (1749-1823), after training in London and a period as an army surgeon, spent his whole career as a country doctor in his native county of Gloucestershire in the West of England. His research was based on careful case-studies and clinical observation more than a hundred years before scientists could explain the viruses themselves. So successful did his innovation prove that by 1840 the British government had banned alternative preventive treatments against smallpox. "Vaccination," the word Jenner invented for his treatment (from the Latin *vacca*, a cow), was adopted by Pasteur for immunization against any disease.

•Christian Charles Schieferdecker, M.D.

Dr. C. G. G. Nittinger's Evils of Vaccination.

Philadelphia: the editor, 1856.

•Because of the lack of clear scientific explanation of its effects, the frequent side-effects, and contaminated vaccines, vaccination itself remained controversial throughout the nineteenth century. It certainly carried risks for the infants being vaccinated, and this volume, playing on parental fears, argued, inter alia, that vaccination was ***nonsensical, unscientific, criminal, and even sinful***. Shown here is a satiric vignette of a protective mother's discussion with the family doctor.

•John Baron, M.D., 1786-1822

The Life of Edward Jenner, M.D., LL.D., F.R.S.

London: Henry Colburn, 1838. 2 volumes.

•While still an apothecary's apprentice in the late 1760s, Jenner had been intrigued by possible relationships between smallpox, cowpox, and swinepox. At the time, he was ***ridiculed***. By 1780, however, he returned to the idea, as evidenced in the conversation recorded here, and in 1789 he experimented by inoculating his own son, then aged one-and-a-half, with the swine pox, followed by conventional smallpox inoculation.