



Enteric Fever: An Israeli perspective

Eyal Meltzer MD DTMH^{1,3} and Eli Schwartz MD DTMH^{2,3}

¹Infectious Disease Unit, ²Center for Geographic Medicine and ³Department of Medicine C, Sheba Medical Center, Tel Hashomer, Israel
Affiliated to Sackler Faculty of Medicine, Tel Aviv University, Ramat Aviv, Israel

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Enteric fever is a systemic infection caused by *Salmonella enterica* serovars Typhi and Paratyphi (with the common synonyms of typhoid fever and paratyphoid fever, according to the causative agent). It was once common in Israel, but for most current practitioners it is a rare and unfamiliar disease. However, the disease is still frequent both regionally and globally; the World Health Organization estimates that some 27 million annual cases of enteric fever occur worldwide, with more than 200,000 fatalities [1]. In the western world two features characterize the current epidemiology of enteric fever: a decline in its incidence and it being mostly a travel-related disease [2,3].

With the ever-increasing number of Israeli travelers to endemic regions and the migration of workers and refugees, there is a need to reacquaint physicians with the disease and its etiology. We describe here the past and current epidemiology of enteric fever in Israel, the salient features of the disease and its causative agents, and discuss in detail current therapy and prevention.

Historic epidemiology of enteric fever in Israel

By the early 20th century, enteric fever was in decline in many industrialized countries but very common in their colonial holdings. In Palestine, with the British occupation and the beginning of mass migration of Jews into the country, more solid data on the local epidemiology of enteric fever began to accumulate. The disease was known locally to be endemic in the region, and was common in the established Arab and Jewish population. Typhoid vaccination was required for all immigrants. However, vaccination did not prevent mass outbreaks and epidemics of enteric fever in several regions, including Tel Aviv and the Jezre'el valley from the 1920s to the 1940s [4]. During the 1950s, probably due to improvements in housing and infrastructure, the incidence of enteric fever declined markedly from about 90/100,000 to about 20/100,000, and has continued to decline to the present day. The last reported outbreak in Israel involved the contamination by sewage of drinking water in the Krayot region (four small towns north of Haifa) in 1985 [5]. This outbreak caused 8000 cases of dysentery and some 80 cases of enteric fever [6]. Since then, due to the universal chlorination of drinking water, enteric fever

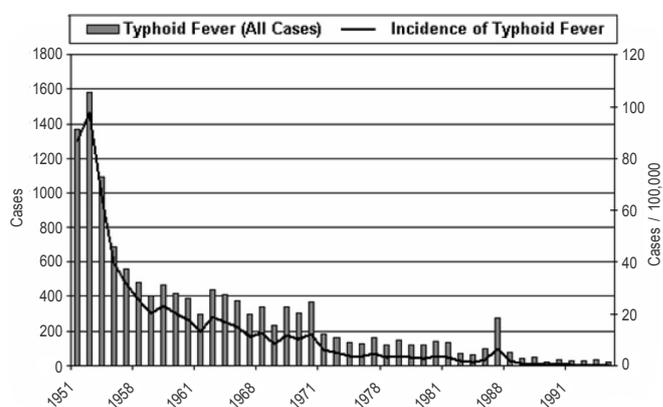


Figure 1. Incidence of typhoid fever in Israel, 1951–1994

became an increasingly rare condition. The immigration of Jews from Ethiopia – a country with a high incidence of the disease – did not change this trend [7]. Figure 1 shows the decline in enteric fever rates in Israel during the last half century.

Current epidemiology of enteric fever in Israel

In a recent study we defined the current incidence and characteristics of enteric fever cases in Israel – both endemic and imported. Since enteric fever is a notifiable disease in Israel, we used the national case registry to study all cases that occurred from 1995 to 2003. Imported and endemic cases were differentiated and specific epidemiological parameters were analyzed [8,9].

As in most other developed countries the majority of cases are now imported; in our study, for the period 1995–2003, 60% of cases were acquired abroad. There are large differences in the likelihood of acquiring enteric fever at different travel destinations [Table 1]. About 75% of imported cases occur in travelers to India and Nepal. Yet it is important to note that several cases were acquired in neighboring countries in the Middle East (i.e., Turkey, Sinai and Jordan), which are usually not perceived as risky areas by Israeli travelers. Most cases occur in Israeli backpackers, and a few are imported by migrant workers newly arrived from abroad [8] or returning from a visit to their homeland.

Table 1. Attack rates of enteric fever in Israeli travelers to various destinations

Country	Incidence of EF cases/10,000 travelers	Local incidence of EF cases/10,000 residents
Egypt	0.03	1.3
Jordan	0.03	0.23
Thailand	0.04	1.57
Morocco	0.07	0.82
Turkey	0.10	0.38
Nepal	0.79	162
India	2.70	98

EF = enteric fever

About 40% of cases are endemic, which is still a relatively high rate of endemic disease in comparison with other developed countries. The overall incidence of endemic enteric fever in Israel was 0.1/100,000. Among the endemic cases the incidence of enteric fever is about three times higher in the Arab population than the Jewish population. The incidence among Jews is nearly unchanged in the last decade, whereas the incidence among Arabs has declined significantly. Cases are evenly distributed geographically, with the exception of Jerusalem where the absolute incidence is twice that in other regions, while the incidence ratio between the ethnic groups remains similar [8]. Reasons for these differences are still unclear. Whether the cases in the Arab population of Israel are truly endemic or imported from adjacent regions – e.g., the West Bank and Gaza, or via *hajj* travel (pilgrimage to Mecca) – needs to be established. It should be borne in mind that the incidence of enteric fever in the Palestinian territories is reported to be 170-fold higher than the rate in Israel [10]. It is hoped that a future analysis of these cases with molecular biology tools will provide insight into these questions.

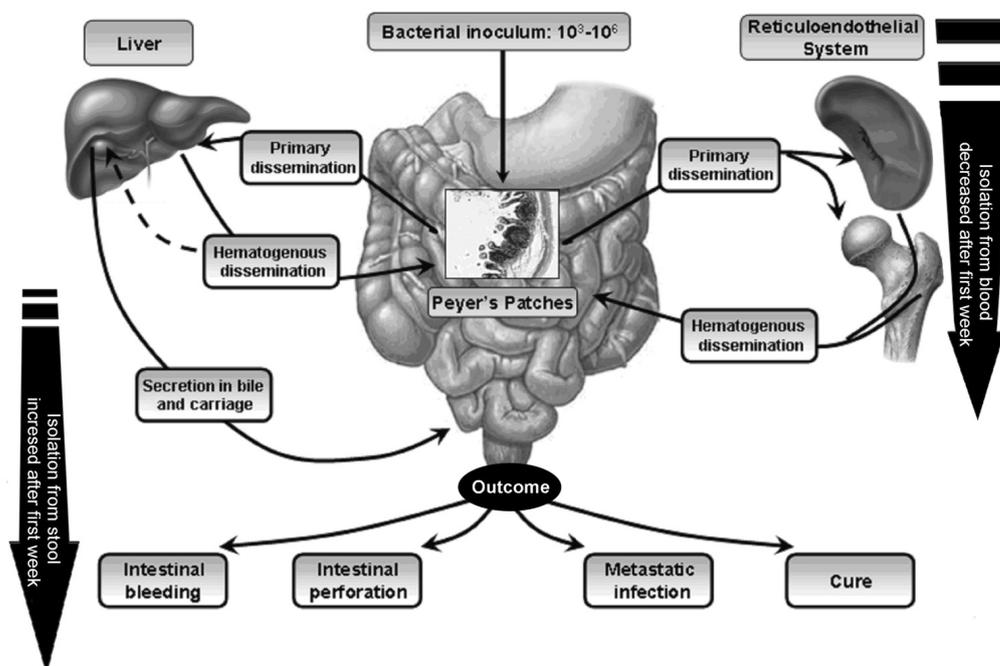
The microbiology of enteric fever

The causative agents of enteric fever are several members of the species *Salmonella enterica*. These are restricted human pathogens, which unlike many other salmonellae do not readily infect poultry, reptiles and mammalian livestock. The main causative agent is *S. typhi*, accounting for 60–80% of cases in most regions [11]. The relative contributions of the three *S. paratyphi* species A, B and C

differ between geographic areas. Thus, *S. paratyphi* A is a common pathogen in the Indian subcontinent [12], while *S. paratyphi* B is found in Indonesia, Malaysia and the Mediterranean region [12–14], and *S. paratyphi* C in Africa [15,16]. In our study we found *S. typhi* to be the causative agent in 80.9% of all cases in Israel. Interestingly, virtually all cases of *S. paratyphi* A were imported, while all cases of *S. paratyphi* B were endemic and restricted to the Jewish population. Among imported cases, we found that prior typhoid vaccination caused a shift in the ratio of typhoid and enteric fever. Vaccination was associated with an increase in the percentage of cases caused by *S. paratyphi* A and a decrease in *S. typhi* cases [9].

Pathogenesis of enteric fever [Figure 2]

Enteric fever-causing organisms can survive in the environment for a significant length of time. The infection is spread through the oral-fecal route: mostly waterborne or via food infected by carriers, and rarely through oral-anal sexual contact [17]. The first step in establishing infection is adhesion to and invasion of the gut wall. About 10^6 bacterial cells are needed to cause infection. Low gastric acidity – as in the elderly – can decrease the infective dose to 10^3 , while prior vaccination can increase it to 10^9 [18]. Dendritic cells that are interlaced in the epithelium overlying Peyer's patches are probably responsible for the internalization of the enteric fever agent. The organisms are able to induce extensive micropinocytosis by mononuclear cells but are able to survive and multiply within them. In this way and through other mechanisms they avoid the more effective elimination by neutrophils. Among others, the Vi antigen of *S. typhi* is important in preventing antibody-mediated opsonization and complement-mediated lysis. Through the induction of cytokine release and

**Figure 2.** Pathogenesis of typhoid fever

mononuclear cell migration and death, the organisms spread throughout the reticuloendothelial system – mainly to the liver, spleen and bone marrow. Usually, within 14 days the bacteria appear in the bloodstream and a symptomatic bacteremic phase ensues. Secondary metastatic foci occur, with splenic abscesses and even endocarditis. Important loci of secondary infection are again Peyer's patches. These are the areas where intestinal bleeding and perforation – the main cause of mortality in the pre-antibiotic era – occur. It is probably during this phase that infection of the gallbladder also occurs. This leads in some patients to long-term (frequently life-long) carriage of *S. typhi* and *S. paratyphi* in bile and secretion to the stool. The exact interplay of cellular and humoral immunity that eventually terminates the bacteremia and ends the disease is not clear. It is known that some HLA types confer relative resistance to enteric fever [19].

Clinical course of enteric fever

Enteric fever caused by *S. typhi*

The first stage of infection and until the establishment of bacteremia is usually a prodromal stage with few symptoms or clinical signs. The initial presentation of enteric fever may be confounded by the fact that co-infection with other pathogens with fecal-oral spread is probably not infrequent when typhoid is acquired in an endemic country. In our series, many travelers infected in India reported initial diarrhea, which in many cases resolved spontaneously prior to therapy. Thus, it may be difficult to establish the exact beginning of symptomatic enteric fever.

The hallmark of the disease is fever. Classically, the temperature rises incrementally during the first few days, and then a persistent fever is established. This is accompanied in many patients with prostration, and an apathetic-lethargic state (the so-called *tuphos* of the ancient Greeks, the source of the terms typhus and typhoid). This typical persistent fever is not frequently noted however, probably due to the wide use of antipyretics [20].

Another feature of the disease is headache, which is common and may be severe. The mechanism causing the headache is not known. In most cases an apathetic-lethargic habitus is present, and in some patients central nervous system symptoms including delirium, psychosis and focal neurological deficits occur, without any evidence of direct CNS involvement in the infection [21]. While secondary pneumonia is a rare occurrence, cough is quite frequent. Since initially few other symptoms exist, a non-specific viral syndrome, as well as malaria and dengue fever are commonly considered initially. When enteric fever is not considered initially on epidemiological grounds this may lead to a delay in diagnosis. Thus in our series, travelers returning with enteric fever from destinations such as Morocco and Turkey were initially diagnosed as suffering from sinusitis or influenza.

In the majority of cases, however, abdominal signs and symptoms eventually appear. These include abdominal pain, constipation, nausea and vomiting. Again, the exact percentage of patients with diarrhea due to enteric fever is hard to establish

and clinicians are advised to consider other co-infections such as giardiasis.

Without treatment, fever and ancillary signs of enteric fever may continue for many weeks, leaving the (historical) patient very weak and debilitated, and prone to other infections. Even with antimicrobial treatment, the temperature does not drop immediately but after a median of about 5–7 days. This probably reflects the relative difficulty in eradicating the organism from its intracellular niche. However, the persistence of fever for a week or more despite antimicrobial therapy should prompt the search for metastatic infection or antimicrobial resistance. In Israel, 1.4% of cases were found with endocarditis and a similar number with splenic abscesses.

A sudden worsening of the abdominal pain should suggest bowel perforation. This feared complication of enteric fever was probably associated with the majority of fatal cases, which in historic reports reached about a third of all cases [20]. Perforation is four times more likely to occur in males than in females [22,23]. With modern therapy this is now a rare occurrence (less than 1% in our series). Massive gastrointestinal bleeding was once another cause of mortality. While the finding of microscopic bleeding to the stool is common, macroscopic bleeding is now rare [24].

The overall mortality of enteric fever with proper treatment is about 1%. In developing countries higher rates are reported, probably reflecting a delay in therapy, a lower nutritional status, or the different case-mix (most cases in countries such as India, Nepal and Thailand are in children) [25].

Relapses can occur, even with appropriate antimicrobial therapy. This again reflects the difficulty in eradicating the organism. In our series 2.2% of patients suffered a bacteriologically proven relapse.

Enteric fever caused by *S. paratyphi*

There are few data on the clinical course and differences between *S. typhi* and *paratyphi* infection. Paratyphoid fever is commonly perceived to be a milder disease [26], but there is little to support this supposition. In fact, in our series the incidence of a complicated course in patients infected with *S. paratyphi* A was even slightly higher than that of *S. typhi* cases.

S. paratyphi B and C appear to be the least studied of the causative agents for enteric fever. In Israel *S. paratyphi* B appears indeed to be a milder condition than *S. typhi*, with a clinical syndrome that is frequently similar to that of non-typhoidal salmonellosis. The proportion of cases occurring in young children was higher, and several cases apparently resolved without antimicrobial therapy. The patients tended to have leukocytosis and not leukopenia, and platelet counts were higher. Even the one fatality attributed to *S. paratyphi* B in our series occurred in an elderly patient with terminal leukemia – again reminiscent of non-typhoidal salmonella bacteremia [8].

Establishing the diagnosis of enteric fever

There is little in the physical examination that can aid clinicians to establish the diagnosis. While all patients are febrile, the temperature pattern is rarely diagnostic. The examination occa-

CNS = central nervous system

sionally reveals relative bradycardia, but this sign is neither universal nor diagnostic (also found in borelliosis, malaria, dengue fever and other conditions). A pink macular rash known as "rose spots" is sometimes found on the torso. This evanescent rash, described as blanching 2–4 mm diameter papules, has been reported in the past in 30–50% of patients [26]. However, rose spots require vigilance and experience to diagnose, and their incidence therefore varies markedly between series. In addition, they are even rarer in *S. paratyphi* A infection [27,28], which is a common pathogen among returned Israeli travelers. In our series, none of 136 patients was diagnosed with this rash. It should be stressed that rose spots are not diagnostic and can occasionally be seen in other enteric infections. Patients frequently have liver and/or splenic enlargement. Electrocardiographic changes in enteric fever patients, usually Q-Tc prolongation, are not infrequent, but rarely does a myocarditis-like syndrome evolve [29].

Most laboratory tests are non-specific. Mild liver function abnormality is common, with a hepatocellular pattern being more frequent. Leukopenia and thrombocytopenia occur, but are neither universal nor diagnostic and may occur in other tropical diseases such as dengue and malaria.

Typically, the eosinophil count should be very low, as should the sedimentation rate. In this respect, a high sedimentation rate may be associated with abscess formation or osteomyelitis, and eosinophilia, if present, should prompt the search for concomitant parasitic infection.

Serological tests for the diagnosis of enteric fever exist (e.g., the Widal test), but low specificity and sensitivity decrease their diagnostic utility. In addition, prior typhoid vaccination may cause a positive test result.

The test for establishing the diagnosis is blood culture. Historically reported as only 50–70% positive, modern culture systems will detect bacteremia in 80–100% of patients [30] (more than 95% in our series). It was already observed a century ago that with increasing disease duration the sensitivity of blood cultures decreases, while stool isolation increases; this probably reflects the process of bacterial localization to Peyer's patches and seeding of the gallbladder [Figure 2]. Thus, stool culture may occasionally be positive even when blood culture is negative. Since prolonged stool carriage of *S. typhi* occurs, the interpretation of a positive stool culture merits caution, and the diagnosis is established only when accompanied by a typical clinical setting.

Bone marrow aspirate and culture is superior to blood culture since the bacterial concentration is 10 times that of peripheral blood. When blood cultures are taken before antimicrobial therapy is started, they will usually be positive and bone marrow culture will not be required. In cases where antibiotic treatment was given prior to hospitalization, bone marrow aspirate may still be positive even if blood cultures are negative [31,32].

Molecular methods for detecting *S. typhi* exist. Detection by polymerase chain reaction in blood and stool samples had a sensitivity and specificity of nearly 100% when compared to culture [30], but this test is not commercially available.

Current treatment – the problem of antimicrobial resistance

Provided that effective antimicrobial therapy is given in a timely manner, the outcome of typhoid fever is usually excellent, with a fatality rate of less than 1% and a low rate of serious complications. This has also been the case in both imported and endemic cases in Israel [8,9].

However, the problem of antimicrobial resistance is as pertinent for *S. typhi* and *paratyphi* as it is for other Gram-negative bacteria, due to their ability to acquire resistance genes by horizontal transmission. Ampicillin, chloramphenicol and trimethoprim-sulphamethoxazole were all highly effective in the past, but there have been increasing reports over recent years of clinical failures due to resistance. Fluoroquinolones have the advantages of very high bioavailability when given orally, high intraleukocytic concentrations and high concentrations in the biliary tract. Although fluoroquinolones were not shown definitely to be more effective than other agents in sensitive strains [33], the prevalent resistance worldwide to ampicillin, chloramphenicol and trimethoprim-sulphamethoxazole has made fluoroquinolones the drug of choice for enteric fever. Unfortunately, within the last decade multiresistant strains, including those resistant to quinolone, have become prevalent mainly in the Indian subcontinent.

In the endemic Israeli strains reported in our series, a multi-resistant phenotype was rare, with many of the strains still sensitive to ampicillin; ceftriaxone and quinolone sensitivity was universal. On the other hand, quinolone-resistant strains were frequently found among returning travelers, especially from 2002 onwards (Eyal Meltzer, unpublished data). Since most imported cases are acquired in the Indian subcontinent, quinolones are no longer recommended as the first drug of choice. Laboratory proof for quinolone sensitivity must rely on minimum inhibitory concentration or by performing disk diffusion test on quinolone and nalidixic acid. Strains that are apparently sensitive to fluoroquinolones but resistant to nalidixic acid should not be considered quinolone sensitive as clinical failure is likely to happen [34]. Thus, the drug of choice for people acquiring the disease in areas endemic to strains resistant to quinolone or nalidixic acid are third-generation cephalosporins such as ceftriaxone. It is a major source of concern that resistance to ceftriaxone is now being reported as well [35]. Another agent that has been shown to be effective against *S. typhi* is azithromycin [36].

The response to therapy in typhoid fever is frequently slow. The time to defervescence usually ranges between 3 and 6 days [31,36], but can be as long as 10 days even when the patient is receiving appropriate therapy and does not have complications [25]. This may be a result of the bacteria's intracellular niche, which is relatively harder to eradicate. Azithromycin, which reaches high intraleukocytic concentrations, may perhaps offer an advantage in therapy, but this remains to be established.

In this respect, the time to defervescence can be a surrogate marker of *in vivo* antimicrobial efficacy. There are several reports associating nalidixic acid resistance with a longer time to defervescence [25]. It has been our impression in recent years that travelers treated with ceftriaxone for typhoid and paratyphoid

tended to respond more slowly to therapy, even though the infecting strains were sensitive *in vitro*, and complications such as abscesses and endocarditis were excluded. Use of combination therapy with azithromycin and cephalosporin may merit consideration, as may the use of aztreonam (currently not marketed in Israel) and carbapenems.

Preventing enteric fever

The basic tenet of enteric fever prevention is better sanitation. Strict separation of sewage from drinking water and chlorination of water (which became obligatory in Israel only after the 1985 outbreak) are the cornerstones of prevention, which led to the marked decline in incidence in the developed countries. Among travelers a strict observance of dietary precautions – avoiding contaminated food and water – has always been stressed. However, the efficacy of these precautions with regard to typhoid has not been established by research and is known to be poor, if judged by their efficacy in preventing traveler's diarrhea [37].

In view of the inefficacy of dietary precautions alone, the need to provide additional protection is clear. The decreased efficacy of many antibiotics makes disease prevention even more important. In cases of prolonged travel, with low living standards and close contact with local inhabitants, the risk of enteric fever may be increased and a higher benefit may be gained from vaccination. However, the best documented risk factor for acquiring the disease is probably geographic – i.e., travel to hyperendemic regions. In Israel, as in the United States and Europe [2,9,38], the majority of all cases are acquired in the Indian subcontinent – India, Nepal, Pakistan and Bangladesh. Indonesia also figures high in some reports. Typhoid vaccination is therefore commonly recommended for all those traveling to developing countries with an intended stay of a month or more, but is recommended for a shorter stay for those traveling to the Indian subcontinent.

To date, three types of typhoid vaccinations exist: live attenuated oral vaccine, with the Ty21a strain (Vivotif®, Berna, Switzerland), Vi capsular polysaccharide vaccine (Typhim Vi®, Aventis Pasteur, USA, and Typherix®, GlaxoSmithKline, Australia), and a new protein-conjugated capsular vaccine. The oral vaccine is no longer marketed in Israel, while the conjugated vaccine is still not available, leaving the inactivated capsular vaccines as the only available option. These vaccines recently became available combined with hepatitis A vaccine (Hepatitisix®, GlaxoSmithKline).

The capsular vaccines are well tolerated, and significant adverse effects are rare. They can be administered from the age of 2 years onwards and are considered effective for 2–3 years, after which revaccination is required. Their major drawback, however, is their relatively poor efficacy. Typhoid vaccination efficacy is usually compared to the whole-cell inactivated vaccine, whose history goes back to the First World War. This vaccine, marketed as a combined vaccine with typhoid and paratyphoid A & B (TAB vaccine), offered effective and comprehensive coverage against enteric fever-causing agents, but local side effects were often significant. A meta-analysis of vaccine trials has shown that Vi

vaccines provide lower protection rates and for a shorter period than the whole-cell vaccine: the 3 year cumulative efficacy was 73% (95% confidence interval 65–80%) for the whole-cell vaccines and 55% (30–71%) for the Vi vaccine [39].

An important caveat is that all estimates of vaccine efficacy are derived from studies on local populations, which may have a degree of preexisting immunity and are likely to have more repeated exposure with immune enhancement than travelers, among whom vaccine efficacy was never clearly established. Here it should be noted that one of the few studies in travelers that provides evidence for the efficacy of typhoid vaccines in travelers involved Israeli travelers. When compared to other western travelers to Nepal who were mostly vaccinated against typhoid, the unvaccinated Israeli travelers were found to have a much higher rate of enteric fever – a rate that approached the reported incidence in the local population [28]. Also, these vaccines offer no protection against *S. paratyphi* A, which is common in the Indian subcontinent. Another, more theoretical concern has been the emergence of Vi antigen-negative strains of *S. typhi*.

The conjugated typhoid capsular vaccine (similar to the conjugated pneumococcal and meningococcal vaccines) has the advantage of increased immunogenicity and higher efficacy but does not address other issues. To date, no new vaccine effective against paratyphoid fever has been developed.

Summary

Typhoid fever is no longer endemic to most developed countries, including Israel. When encountered, it usually occurs in travelers returning from endemic countries. Worldwide, the disease is far from being eradicated. It is still highly prevalent in some popular travel destinations such as India. With the continued increase in Israelis traveling to (and in migrant workers arriving from) endemic regions, physicians in Israel should be well acquainted with the disease. Unfortunately, with the limited efficacy of the current typhoid vaccinations and the increase in multidrug-resistant strains, cases among travelers are expected to continue to increase and become ever challenging to treat.

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Correspondence: Dr. E. Schwartz, Center for Geographic Medicine and Dept. of Medicine C, Sheba Medical Center, Tel Hashomer 52621, Israel.
 Phone: (972-3) 530-2186
 Fax: (972-3) 530-2011
 email: elischwa@post.tau.ac.il

If stockmarket experts were so expert, they would be buying stock, not selling advice

Norman R. Augustine (1935-), U.S. aircraft engineer and industrialist