Introduction:

If you stray from the island's main road into the rolling and reeling country lanes, you are bound to come across chapels in Malta, built during the time of the Knights Hospitallers of the Order of St. John (also commonly known as the Knights of Malta), which bear the inscription in Italian: "Non gode l'immunità ecclesiastica", this sanctuary does not enjoy ecclesiastical immunity.

The Latin word munus denoted obligations and services which cities and persons in days gone by had to give their Lords and Masters; on occasions they were given dispensation from these obligations, that is to say they were granted immunity and so today we have adopted the word immunity to denote freedom from disease.

One can safely assume that early in the evolutionary history of our species our forefathers and our female ancestors (I do not think that there is such a word in the English tongue as foremothers, at least not in Fowler's) must have observed that when one of their offspring recovered from a disease that particular visitation of the gods did not seem to recur in the same member of their brood. In like manner this paper sets out to show that when we inoculate the familiar inactivated typhoid vaccine and cholera vaccine, or when we administer orally these attenuated (live) or inactivated (dead) vaccines, or chemical extracts or fractions thereof, we are attempting to reproduce as faithfully and as closely as we can the conditions which we have observed result as a consequence of a natural infection by the enteric bacilli and the cholera vibrios.

I can illustrate this point by reference to the organisation in which I serve. Proposition: What are the functions of the Army? Answer: The functions of the Army in wartime (and I can almost hear the resonant wartime Churchillian mot- tos) is to destroy the enemy swiftly, utterly and effectively with as little trauma to oneself as possible; the functions of the soldiery in peacetime is an insurance and a deterrent to ensure that unfriendly aliens and foreign powers do not trespass and encroach upon our Lebensraum. Applying the principles of war to immunology, if your Maginot line, i.e. that wonderful organ the skin, has been breached by the fangs of an animal and the rabies virus has been deposited within your peripheral defences, you employ a similar army of other rabies viruses to intercept the raiders before they reach your administrative capital — the Central Nervous System; and once again if your body has been invaded by the variola virus you bring in a mercenary army of the closely related vaccinia pox virus to help you overthrow and cast out the invader. These are warlike activities, the parallel in peace time activities are the occasions when you...
so prime and train your patient's personal bodyguard and defence forces that he or she will stand a good chance of fending off all inimical agents and even if invaded will not suffer the full and possibly even fatal consequences of being a foolish immunologic virgin in respect of that particular invading micro-organism such as the enteric bacillus or the cholera vibrio which are the subjects of this study.

Section 1 — Typhoid, Paratyphoid A, Paratyphoid B, vaccines

ARMIES AND TYPHOID

FANCO-PRUSSIAN WAR =
SPANISH-AMERICAN WAR =
BRITISH-BOER WAR =

Long before these vaccines came on the market, even before the dawn of bacteriology itself, armies and typhoid had been a natural twosome, as closely associated together and never distant one from the other as Naomi and Ruth, it is therefore gratifying to me as an RAMC officer to state that the first typhoid vaccine, certainly in the English speaking country, was prepared in the laboratories of our own army medical school attached to the Royal Victoria Hospital, Netley, on the beautiful stretch of Southampton Water.

TYPHOID VACCINE 1896

WRIGHT & SEMPLE PFEIFFER & KOLLE
UK GERMANY
12 Nov 1896

The story behind the story is that some time after David Bruce, ably aided by his consort, had discovered the Micrococcus melitensis in the spleen of a soldier in Malta. Almroth Wright, (Fig 1) the Professor of Pathology at the Army Medical School was visited by Haffkine (c. 1893) who demonstrated to the Netley workers how he prepared his cholera vaccine which he intended to use on a grand scale in India. Now the reader will recall that Haffkine was a pupil of Pasteur and therefore followed his Master's technique of giving a first dose of an attenuated vaccine followed by a second dose of a virulent organism (virus fixé). Wright was impressed and inoculated himself first with a dead brucella suspension and subsequently with a live brucella suspension, and he duly went down with a severe attack of brucellosis or Malta Fever as it was called in those days; during his protracted convalescence he had plenty of time to think on armies and

60% of German casualties
20,000 cases in U.S.A. Camps
9,000 deaths (Total strength 200,000)

Fig. 1.

ALMORTH WRIGHT (1861-1947). Professor of Pathology, Army Medical School, Netley, Southampton; introduced Typhoid vaccine. An enthusiastic exponent of vaccine prophylaxis and vaccine therapy, 'the physician of the future will take upon himself the role of an immunizer.'
William Boog Leishman. Professor of Army Pathology (1903-1914) Director of Army Pathology (1919-1923). A great advocate of TAB vaccine.

Typhoid and nothing daunted by his dire experience with his brucella vaccine he turned his thoughts to the preparation of a typhoid vaccine to give protection against the disease which was so obviously of great military importance. Eventually he did produce a typhoid vaccine by growing the bacillus in broth and killing the organism by heat. However, the Army did not accept with unreserved rapture an inoculation on which on occasions gave ferocious reactions and the efficacy of which was open to considerable dispute, so the Government resorted to a political strategy by offering Wright a knighthood which after some hesitation he accepted in 1906. This raised up the vaccinator-pathologist stature — it is a fact of life that the higher one goes up in Army rank and no doubt mutatis mutandis the same law applies in a civilian milieu, people are that much more ready to listen to what one has to say — c'est la vie! The typhoid vaccine got well under way, in 1915 W.B. Leishman (Fig 2) incorporated that para A and para B components so that we had in World War I our familiar TAB vaccine. It has had a chequered history as for example the Army was persuaded by A. Felix (Fig 3), who advocated the importance of the Vi antigen described by him and Margaret Pitts, to produce an alcoholised vaccine towards the end of World War II. However, in the Middle East we in the Services were rather jolted when epidemics of enteric fever occurred in personnel who had been fully vaccinated mostly however with the alcoholised vaccine, so we reverted back again to the 'Leishman' phenolised vaccine.

Fig. 2.

William Boog Leishman. Professor of Army Pathology (1903-1914) Director of Army Pathology (1919-1923). A great advocate of TAB vaccine.

Fig. 3.

Arthur Felix (1887-1956). His numerous studies on the Vi-antigen of typhoid bacillus led to a replacement of the old classical vaccine by Vi-containing typhoid vaccine.
Our belief that the presently available typhoid vaccine is effective is based on field trials carried out in Yugoslavia (1960—1963), Guyana (1960-1967), Poland (1961-1967) and the USSR (1962-1965) which show that the heat-killed phenol preserved vaccines give about 70% protection for 2–3 years, and the acetone killed vaccines are slightly more efficacious. The reader must realise that this statement refers to the typhoid vaccine only, there have been field trials using para B vaccines and these have shown that this vaccine also gives a 70% protection if given in appropriate dosage. Less work has been done with the para A component, many authorities feel that it is not really worthwhile to incorporate the para A and para B elements in a compound vaccine as this appears to increase the reactogenicity of the triple vaccine and so would rather recommend a typhoid vaccine for general use, incorporating the para A and para B components according to the geographic areas where these two enteric diseases give rise to concern because of their attack rates.

The Armed Forces Medical Services have also been instrumental in the introduction to the U.K. of TAB vaccine given in 0.1 ml doses by the intradermal route; this was first used at the time of the Suez crises in 1956 for booster doses, and four years later was adopted also for the primary basic immunisation schedules using 0.1 ml doses injected in the deltoid region of the shoulder.

**CHOLERA VACCINE**

This is the doyen of human bacterial vaccine; it was as far as I can make out the first human bacterial vaccine and was introduced in the mid-1880’s by Jaime Ferran y Clua, a Spanish ophthalmologist/}

<table>
<thead>
<tr>
<th>Year</th>
<th>No at Risk</th>
<th>Vaccinated</th>
<th>Typhoid Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>1945</td>
<td>750</td>
<td>91%</td>
<td>110</td>
</tr>
<tr>
<td>1950</td>
<td>657</td>
<td>100%</td>
<td>84</td>
</tr>
</tbody>
</table>

From R.L. HUCKSTEP (1962) TYPHOID FEVER.
Fig. 4.

WALDEMAR MORDECAI HAFFKINE (1860-1930). A Russian Jew, a member on the staff of the French Pasteur Institute in Paris, who went to British India to vaccinate successfully with his cholera vaccine on grand scale.

ml; and it is important to have both the Inaba (antigens AC) and the Ogawa (antigens AB) components as there is not enough heterologous cross protection between these two serotypes both of which must therefore be incorporated in the vaccine. Since the El Tor biotype (note: not a a serotype) at present waving its tentacles widely over Asia, Europe and Africa possesses the same antigens (ABC) as the classical Inaba and Ogawa organisms the presently available cholera vaccine affords equal protection against 'classic' cholera as it does against EL Tor cholera.

Section 3. COMBINED VACCINES

For the convenience of travellers and holidaymakers, and tourists a combined TAB/CHO vaccine is available commercially. In the armed forces we use regularly a triple vaccine TAB which is moreover mixed with Tetanus Toxo.d, the combined TABT being particularly suited to our requirements; in many countries the cost benefit of community preventive medicine by means of vaccine is considerably enhanced by incorporating multiple components in a quadruple vaccine such as Typh-Per-Diph-Tet Vacc or TAB-Dip-Tet-Vacc.

One cloud threatens to disturb the simultaneous vaccination programmes of recent years so greatly favoured in the developing countries and that is the observation that cholera and yellow fever vaccines, and also cholera and measles vaccine are somewhat mutually antagonistic as seen by the depression in the expected antibody responses after immunisation; this is a worrying problem and needs to be investigated further in the near future, one has to note that measles is one of the worst killers in some areas of the world where cholera has mounted in the past four years a full scale attack for the first time in recorded medical history. Another trap for the unwary which I have not personally seen but which is stated to exist is the rise after Cholera vaccination of antibodies cross-reacting with other organisms thus leading possibly to mis-diagnosis, for examples of Brucellosis.

Section 4.

THE SHAPE OF THINGS TO COME
‘Natura non vincitur nisi parendo’
(A. Besredka 1926)
(Fig 5)

In many of our medical textbooks typho.d and cholera are usually grouped together in one and the same section because they are considered as being both intestinal diseases; from the point of view of pathologists, phys.ologists, immunologists and microbiologists no two diseases could be so far apart as these two so called in-
ALEXANDER BESREDKA (1870-1940). A great protagonist of oral vaccines, 'Natura non vinci nisi parendo'.

testinal diseases.

Consider the pathogenesis of typhoid, the bacilli penetrate through the alimentary tract, permeate into the lymphatic tissues, make their way into the blood vascular system, get disseminated all over the human body and are temporarily obstructed and taken up by the various strategically placed foci of the reticulo-endothelium system. Here they increase and multiply and re-emerge once again in the blood circulation to give rise to the signs and symptoms of typhoid fever; this infection therefore should be more rightly regarded as a typhoid septicaemia and not as a local intestinal disease, and it follows that anti-bacterial antibodies produced as a result of typhoid vaccine will prevent the onward progress and widespread dissemination of the bacilli though admittedly one has to realise that the bacillus is a facultative intra-cellular parasite and no doubt cellular immunity, beside humoral immunity, has a part to play.

On the other hand the vibrio is a non-invasive organism, it simply gets itself absorbed like a limpet to the mucosa of the intestinal tract and (unlike shigella organisms) never even penetrates the epithelium. It is only in the past decade that we have learned that here in the closest apposition possible to the living epithelium the cholera vibrio liberates a toxin, if one can call it that, and causes a toxnosis rather than a true infection. The cholera victim succumbs to a combined loss of water and electrolyte imbalance. The toxin has been identified, purified and even obtained in a crystalline state by U.S.A. workers, and it will not come as a surprise to the reader that a toxoid vaccine has been duly prepared, as had been done years ago with diphtheria and tetanus toxin. Unfortunately the first trials of formalised toxoid in human volunteers resulted in some reactions attributed to the fact that the toxoid had reverted to toxin on injection into human tissue, however it is possible that the more recent 'glutaraldehyde' toxoid still under investigation may get over this difficulty. Thus in future we may well have a combined bacterial-toxoid vaccine consisting of a bacillary suspension suspended in toxoid fluid so as to give protection both against the vibrios and also against their secreted exo-enterotoxin.

PARENTERAL ENTERIC VACCINES

1. None are wholly satisfactory
2. Lacking in efficacy
3. Duration inadequate
4. Side reactions

WHO Techn Rep Ser No 500, 1972.

Despite the fundamental difference in the pathophysiology of these two diseases they do have one thing in common, namely their portal of entry which is the alimentary tract, "you can eat typhoid and cholera, you can drink typhoid and cholera; but you cannot catch typhoid and cholera". It was therefore to be expected
COLONEL D MEL of the Yugoslavian Army Medical Academy, has worked brilliantly on attenuated streptomycin dependent vaccines.

that many attempts would have been in the past, and are still being made in our day to produce an efficacious oral vaccine against these two diseases. Thus live typhoid bacillary suspensions on the well known lines laid down by Colonel David Mel (Fig 6) of the Yugoslavia Army where he led the field with a successful streptomycin dependent bacillary dysentery vaccine; the latest live typhoid vaccine to come to the centre of the stage is prepared from enzyme (ep’merase) deficient mutants, and these hold much promise though much more work is needed before their wide adoption. Working with ‘live vaccine the manufacturers and the licensing authorities have to be extra careful all along the line of production, distribution, administration and follow-up. The live vaccines are always antigenically and immunologically better performers than the ‘dead’ vaccines, yet because of the easier and less risky method of production and administration it is these inactivated vaccines that are in actual use in some countries — this in the German army a course of 3 pills for 3 days (Typhoral is recommended as a basic primary immunisation schedule, with booster doses given yearly.

Similarly the same qualifications apply to oral cholera vaccines — live bacilli either found naturally as non-pathogens such as the El Tor Water vibrio of Mukerjee, or artificially manipulated and produced in the laboratory by genetic bio-engineering and chemical mutagens have been shown to give protection; and again inactivated vaccines have also been tried with some degree of success but the safe and well tried preparation of inactivated cholera vaccine given parenterally still is the leader in this field and is the one to be recommended even though as has been stated before it is a rather inefficient bacterial vaccine. It may be that we expect too much of the cholera vaccine since repeated infections of cholera can follow even a natural infection.

It may well be that in future we will resort to the utilization of both routes of administration — basic parental course of inactivated vaccine to stimulate in general the systemic immunologic system followed by regular boosters of inactivated or attenuated vaccine given orally to act as a stimulant to the local immunologic system serving the intestinal tract.

SECTION 5 — The Indications

I assume that the readers perusing this essay can be divided, like Caesar’s Gaul into 3 parts, namely those in favour of these vaccines, those who do not recommend them at all, and a third group who perhaps use them on occasions if specially asked for by a persistent patient or an equally insistent in — law. For the first group of readers no explanation is needed,
for the second group of readers no further explanations are possible, but for the benefit of the third group who sit on the fence and watch which way the wind is blowing, the following list of indications for the use of these vaccines is appended in the hope that it may be of some help to them in their dilemmas.

**INDICATIONS FOR TYPHOID: CHOLERA VACCINATION**

- Persons travelling to endemic areas.
- In areas of high endemic incidence.
- In face of epidemics, disasters, floods etc.
- For medical and paramedical personnel.
- For the armed forces, missionaries, voluntary service overseas personnel.
- Family contacts of chronic carrier.

**SECTION 6 — The Epilogue**

It seems to be so many years ago that I bravely attempted to define the ideal vaccine in the following words:

*The Immunologic Pill*

The ideal vaccine is one that:
1. Confers long life protection
2. Causes no harmful local systemic reactions
3. Is given in one small single oral dose

J. Hyg 1963

Lead, kindly light, for we are still far from home!

**Acknowledgements:**

I am indebted to many workers and writers in the field covered by this essay, too numerous to mention.