one affected happened to have been shut off from communication with the other by inflammation at an early stage of the disease. The occasional phenomenon of many exaggerated reflexes is no doubt due to paralysis of higher controlling centres.

So striking are these random lesions of the nervous system that cases of pure throat affection have not been regarded as cases of the disease at all. The initial catarrh is so quickly got over that it is often ignored by the patient, or he imagines it to be his usual condition, due to smoking or to some other cause. But all the time toxin is being gradually absorbed, and at length it reaches the nervous system and depresses it, and thus the way is prepared for a general advance. Then, on the occurrence of any severe depression, a sudden change takes place, and the disease is then called fulminating. Why a fulmination takes place is not an easy matter to explain. Some cases develop all the serious aspects at once, and yet get well. The cerebro-spinal fluid at this stage is sometimes reduced so much that only a few drops can be got, but they usually contain pus cells and many organisms. A negative pressure has been alleged in these cases, but no air rushes into the cannula, while the few drops exude without suction. In these cases a reduction of the normal amount of fluid has taken place, and such cases are severe, and a second puncture gives an excess of fluid which is usually purulent.

Other cases give a clear fluid which is sterile. It contains no pus or formed matter at all on centrifugalization. But it has only once been found to be normal, in a chemical sense. Normal cerebro-spinal fluid contains dextrose 5 per cent., salts, and about 0.02 per cent. globulin. All these fluids contained an excess of albumin or albumose, and in the cases examined for sugar there was a loss of sugar, but never complete absence of it. Normal cerebro-spinal fluid is rendered pink by the addition of a 1 in 1,000 solution of potassium permanganate, and remains pink for at least five minutes, but in meningitis the clear fluid promptly becomes yellow. This is not due to reduction by glucose, but may be due to reduction of a glucose fermentation product, which must be the result of enzyme action, as there are no living organisms in the fluid.

The pathological process, then, seems to be this:

1. Local infection (that is, Stage 1).
2. General infection (that is, Stage 2). Toxic action on the nervous system, with excretion or escape of albumin into the cerebro-spinal fluid, transforming it into a culture medium for the invading organisms.
3. Breakdown of the defences of the meninges and general advance (that is, Stage 3). Occasionally the entrance of organisms to the cerebro-spinal fluid takes place early, accompanied by apparent absorption of fluid; but the general rule seems to be for an accumulation of sterile fluid first to take place, and then a breakdown of the defences, accelerated by the pressure of the fluid, and it therefore seems to be advisable to puncture early to prevent the occurrence of the final stage. The accidental escape of blood into the meninges would probably do good by supplying antibody where it is naturally deficient.

As regards the pain inflicted by puncture, it is quite tolerable when the operation is done skilfully, and in partially stuporose cases it seems to be totally ignored. In those cases in which the fluid happens to be clear and sterile, the relief of the headache is so marked that one patient made the observation that it was well worth suffering the pain of puncture to obtain the relief of headache which immediately followed it.

Sequelae of Puncture.—None have been observed yet. Sepsis, of course, should never occur, and in this Command Isolation Hospital it is unknown, although cases are sometimes punctured every day.

The Amount of Fluid to Remove.—As much as will come is a good rule. Three or four ounces can safely be removed. Early and frequent puncture has undoubtedly saved many lives, but this is encroaching on the question of treatment.

Number puncture in competent hands is always justifiable, and it gives the only criterion by which to diagnose the third stage of the disease. In fact, not a case yet notified in this Command has failed to present pus and meningococci in the cerebro-spinal fluid, and only such cases have been regarded in estimating the mortality. All sterile cases have been put in another category, awaiting a satisfactory nomenclature of the disease.

PROPHYLACTIC INOCULATION AGAINST TUBERCULOSIS.

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SINCE tuberculosis is, next to old age, the chief cause of death in these countries, there is no need to justify the assertion that some further measure or measures are necessary in dealing with the disease.

It is generally agreed that practically every one who has attained adult years has been infected by the microbe, and a large proportion show healed lesions *post mortem*. For instance, Hamburger and Monti investigated in Vienna the question on a large scale by means of skin and subcutaneous tuberculin reactions, and found that 95 per cent. of children who attained the age of 11 to 16 years were infected.

There are two ways in which a disease may be dealt with: (1) The microbe may be prevented from attaining access to the individual; (2) the individual may be rendered an unsuitable environment for the microbe to grow in.

Since under present conditions the infection is so universal, it would appear impossible to prevent the infection attaining access to the individual, although it is obvious that more might be done to prevent direct infection from the diseased, both human and bovine.

Taking Vienna again as an example, it is shown that while, as I have said, 95 per cent. get infected, only 15 per cent. develop tuberculous disease to a serious extent. That is, only in this percentage is the soil suitable for the continued growth of the bacillus. We must assume that in this proportion of the inhabitants (20 per cent.) the resistance to the disease is subnormal. If we could make the resistance of these to the disease equal to that of the 80 per cent., the problem would be solved, and the disease would occur only sporadically.

The development of the disease in the 15 per cent. may be due to:

- I. Bad hygienic surroundings.
- II. Lowered resistance due to infection with other microbes.
- III. Inherited low resistance.
- IV. Overcoming of a normal resistance by a virulent or continuous infection.

I. *Environment.*—The effect of bad environment is well illustrated by figures of tuberculosis mortality among the different classes in the Dublin registration area for 1912:

Professional and independent classes	... 0.41 per 1,000
Middle class	... 1.92 "
Artisans and small shopkeepers...	... 2.94 "
General service classes	... 3.16 "

We may take the middle class as having reasonable hygienic surroundings, and being people who are likely to die at home, so that good hygienic surroundings will not produce the desired result. Something further is necessary.

II. *Resistance Lowered by other Microbes.*—It is common knowledge that in children such infections as measles and whooping cough predispose to tuberculosis. More important, as far as pulmonary disease is concerned, are catarrhs of the respiratory tract brought about by the catarrhal microbes. The onset is constantly traced to acute or chronic catarrh, which is the primary infection, and not the tuberculosis. Frequently the ordinary methods of treatment entirely fail to cure the patient of these catarrhs. In my opinion it is seldom that tuberculosis of the lungs is not due to a mixed infection, and for successful treatment it is essential to deal specifically with the accompanying catarrhal microbes, as well as with the tubercle bacillus. It is, therefore, very important not to allow a catarrhal infection to become chronic. It is comparatively easy to clear off these infections with autogenous vaccines. However, while these catarrhal microbes are important help-meets of the tubercle bacillus, yet increasing the patient's resistance to them will not give the same guarantee against the disease as putting up the resistance to the tubercle bacillus itself.

III. *Inherited Low Resistance.*—I do not know whether the opinion that children of tuberculous persons inherit a

low resistance, or the opinion that they are more likely to get the disease owing to greater opportunities for infection, holds the field at present. For my present purpose it does not matter much. My own opinion is that a low resistance is inherited. *A priori*, it seems unreasonable to suppose that germ cells inhabiting a person poisoned with tubercle toxin should not participate in the poisoning effect and hand on its lowered resistance, especially if the infected parent is the mother. This point has been investigated statistically by Karl Pearson, who writes as follows:

It is impossible to examine such data . . . without being impressed with the importance of the constitutional factor in this matter, and although the constitutional factor may without doubt be weakened by a wide variety of causes, our investigations in the eugenics laboratory show it to be in the main and on the average of large numbers a question of inheritance. That clinically obvious and apparent tuberculosis appears to be inherited at precisely the same rate as stature or cubit or insanity, impressed me at the outset as remarkable evidence for the constitutional immunity factor being of more importance than the infection factor.

It does not seem necessary to bring forward further evidence on this point.

IV. Virulent or Continuous Infection.—A normal resistance may be overcome by a massive or continuous infection with virulent microbes. There can be no doubt as to the variability of the tubercle bacillus with regard to virulence; it is the experience of every laboratory worker. One of the most potent ways of increasing the virulence of microbes is to pass them through a series of animals with low resistance. So that if a person of low resistance gets the disease he is likely to pass on a more virulent strain. A normal resistance in every individual, human or bovine, would tend to reduce the virulence of the tubercle bacillus, so that a normal resistance would suffice to protect the individual.

There is only one method of bringing up a low resistance to normal or of increasing a normal resistance, and that is the production of specific antibodies or of a mechanism facile in the production of these antibodies in the individual by inoculating him with a vaccine of that particular microbe. In the case of a universal infection like tuberculosis, it is the one measure that will protect when the constitutional resistance is lowered by the various environmental and inherited causes of low resistance.

There is plenty of precedent for such a measure. Witness the success with regard to low incidence and death-rate brought about by preventive inoculation against typhoid fever and the marked reduction in the incidence of pneumonia by the prophylactic use of vaccine amongst the native workers in the mines in South Africa.

Is there experimental evidence that inoculation with tuberculin of various sorts conveys any immunity against the tubercle bacillus when artificially injected? It is true that with most of the antigens so far used no complete immunity has been obtained. At the best only a retardation of the fatal result. But the conditions of artificial infection with large amounts of living bacilli, causing a sudden and overwhelming strain on the immunizing mechanism, are very different from the natural infection, where at the most a comparatively few microbes have to get so acclimatized that they can develop to such an extent as to produce evident disease. If these considerations are correct, partial immunity is all that is necessary under natural conditions.

None of the serological tests so far designed to give evidence of the extent of the immunity that can be produced are satisfactory. Wright found the opsonic index of little or no value in gauging his antipneumococcic dosage. Recent work has demonstrated that patients obviously dying of tuberculosis gave large complement fixation. So far as I am aware, there is no test of value for anti-endotoxin such as can be used for antitoxin, and it must not be forgotten that when immunity is most complete it is a cellular one with no discoverable antitoxin or other antibody in the blood. This is well known in the case of production of antidiphtherial and antitetanic serums, where the animal may be completely immune and yet have no antibodies in the serum.

The only real test of production of sufficient immunity after prophylactic inoculation is the reduction of case incidence and possibly of case mortality.

It has been my practice for the last eight years to urge the members of families whose parents were tuberculous, or in which cases of tuberculosis had occurred, to undergo a short course of tuberculin. The tuberculin I have used until lately is Koch's T.R., and the doses I have used for adults have been, as a rule, 0.001 c.mm., 0.005 c.mm., and 0.01 c.mm. For infants 3 months old 0.0001 c.mm., 0.0005 c.mm., 0.001 c.mm. Sometimes further doses are given. There is sometimes a slight rise of temperature in the evening if the injection has been given in the morning, but otherwise no serious disability. The usual interval is seven days. The improvement in health in many of the members of tuberculous families I have thus treated has been most satisfactory, and so far no case has occurred among those who have been inoculated, but the numbers are far too small to have any value.

T.R., however, is not a very good antigen, nor are any of the ordinary tuberculins on the market. Some years ago I was fortunate in discovering that tubercle bacilli would dissolve in benzoyl chloride, and that this solution produced very marked focal and general reactions in tuberculous patients. When using it for therapeutic purposes, the initial dose had to be very small—0.0000001 mg. in lung cases, 0.000001 mg. in extra-pulmonary cases. The highest dose that had to be attained was 0.01 mg. The clinical results have been so satisfactory that I now use no other for therapeutic purposes. The doses are increased as follows: 0.0000002, 0.0000004, 0.0000006, 0.0000008, 0.000001, and so on. The dilutions are made in liquid paraffin, containing 2 per cent. benzoyl chloride, and I generally add 0.032 gram iodoform dissolved in ether, so as to combine immuno- and chemo-therapy.

For prophylactic purposes the initial doses may be larger and the rises more rapid. At present I use the following series: 0.000001, 0.00001, 0.0001, 0.001 for infants; 0.00001, 0.0001, 0.001, 0.01 for older children; for adults an additional dose 0.1 may be used. The usual interval is a week. If after the initial dose there is a marked reaction, focal or general, then the immunization must be more carefully carried out, using the increments of dosage prescribed for treatment.

Many methods have been used to obtain free endotoxin for antigenic purposes, such as grinding frozen microbes, allowing them to undergo autolysis in distilled water, treating them with antisera, and so on; some of these have been successful. Von Ruck has produced an antigen by grinding tubercle bacilli and extracting them with different fluids, combining the substances extracted in certain proportions. He reports good experimental and clinical results. I hear that Moss has produced a solution of bacilli in lactic acid, but I have not seen his paper.

The benzoyl chloride solution is very easily made. Ten milligrams living tubercle bacilli from the heaped-up growth in Dorset egg medium are weighed on an accurate chemical balance. The weighing is done on the under surface of the glass stopper of the bottle containing the 10 c.cm. of benzoyl chloride they are to be dissolved in. The masses of bacilli are broken up and mixed with a little of the benzoyl chloride on the stopper. The stopper is then inserted into the bottle and shaken down into the fluid, which turns milky. The bottle is put in the incubator for twelve hours, and is shaken occasionally. The fluid gradually clears. The stock solution appears to keep a long time.

My opinion, then, is that, while I think every one ought to be inoculated against this disease so as to make sure their resistance is at least normal, a beginning might be made with members of families in which tuberculosis has occurred, since their resistance is usually subnormal and they have peculiar facilities for contracting the disease. Experience alone will teach us the value of the measure, the best antigen to use and the best average dosage, and the experiment, while necessarily prolonged, is perfectly harmless and inexpensive; it might be extended by inoculating calves, and thus attempting to cut off the bovine source of infection.

DR. LANGLET, Mayor of Rheims, who was recently decorated with the Cross of the Legion of Honour and mentioned in dispatches for his conduct during the bombardment, has been awarded the Audiffred prize of £600 by the Académie des Sciences Morales et Politiques, in recognition of his devotion to public duty.