

I have encountered many cases of umbilical hernia in children who were also suffering from repeated attacks of abdominal pain, but in every case the pain was due to other causes, generally to appendicitis. I have never encountered a case in which an umbilical hernia has been the cause of abdominal pain.

Diaphragmatic Hernia.

There are several varieties of diaphragmatic hernia; but the one giving rise to attacks of abdominal pain and vomiting is that in which the stomach, or portion of it, periodically passes through the oesophageal hiatus. This condition must therefore always be suspected when there is a history of repeated attacks of upper abdominal pain associated with vomiting and dyspnoea.

Some time ago I saw and successfully treated a girl, whose attacks had commenced in early infancy, and the trouble was not diagnosed until she reached the age of nine years. I was able to close the enlarged oesophageal hiatus in this patient through an incision parallel to and about one inch below the left costal margin.

Gastric and Duodenal Ulcers in Infants and Children.

Peptic ulcer is very rare in children. The rarity has been attributed to the small amount of acid in the gastric secretions of children, and to the motility and rapid emptying of the stomach.

Recently two patients, one suffering from gastric and the other from duodenal ulcer, were admitted to the Royal Alexandra Hospital for Children. Both were girls, one aged three and a half, and the other aged seven years. The first child vomited a large amount of blood over a period of twenty-four hours, and died as the result of hæmorrhage, twenty-four hours after her admission to hospital. *Post mortem* a small ulcer was discovered in the pyloric region of the stomach. The second patient had several attacks of hæmatemesis, associated with severe abdominal pain, over a period of two years. A duodenal ulcer was revealed by X-ray examination and the child recovered after treatment by diet and alkalis.

Recently a baby, aged twenty-four hours, died after severe hæmatemesis at the Royal Hospital for Women, Paddington. The early age and the failure of response to treatment, proved that the lesion was not hæmorrhagic disease of the new-born. At post-mortem examination a tiny excavated ulcer was found in the pyloric region of the stomach.

Downes⁽¹⁾ reported a case of perforation of a duodenal ulcer in a child, aged three years; a diagnosis of acute appendicitis had been made. Koplik,⁽²⁾ quoted by Lockwood, reported one case of peptic ulcer in 300,000 of diseases in children.

Holt⁽³⁾ quotes four cases of duodenal ulcer in young infants, all on the posterior wall of the duodenum just below the pyloric ring; all were round, punched-out ulcers.

I believe that in many cases of duodenal ulceration in young infants, some other condition is present interfering with the proper functioning of the duodenum, such as duodenal ileus due to pressure of the superior mesenteric artery; this itself is due to the drag of the small bowel attached by a very narrow mesentery.

Conclusion.

Finally, before coming to a conclusion as to the diagnosis of an acute abdominal condition, we must always exclude painful conditions in other parts. We all know how easy it is to fall into the error of diagnosing appendicitis, when the real trouble is renal or ureteral colic. Pneumonia and diaphragmatic pleurisy are often diagnosed as acute appendicitis; and I have encountered cases in which acute *otitis media* has been diagnosed as an acute abdominal condition. Such mistakes are more common in young children than in adults.

References.

- ⁽¹⁾ H. L. Barnett, A. F. Hartmann, A. M. Perley and M. B. Ruhoff: "The Treatment of Pneumococcus Infections in Infants and Children with Sulphapyridine", *The Journal of the American Medical Association*, Volume CXII, February 11, 1939, page 518.
- ⁽²⁾ P. L. Hipsley: "The Treatment of Intussusception", *THE MEDICAL JOURNAL OF AUSTRALIA*, November 24, 1934, page 696.

⁽³⁾ P. L. Hipsley: "Two Cases of Non-Rotation of the Mid-Gut Loop in Children", *The Australian and New Zealand Journal of Surgery*, Volume IX, Number 1, July, 1939, page 79.

⁽⁴⁾ W. A. Downes: "Perforated Duodenal Ulcer", *Annals of Surgery*, Volume LXXVII, 1923, page 756.

⁽⁵⁾ C. D. Lockwood: "Ulcer of the Stomach in Children, Before Puberty", *Surgery, Gynecology and Obstetrics*, Volume XIX, 1914, page 462.

⁽⁶⁾ L. E. Holt: "Four Cases of Duodenal Ulcer in Infants", *The American Journal of Obstetrics*, Volume LXVIII, 1913, page 169.

THE RESULTS OF INTRANASAL INOCULATION OF MODIFIED AND UNMODIFIED INFLUENZA VIRUS STRAINS IN HUMAN VOLUNTEERS.

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It is now fully established that the great majority of typical influenza epidemics are due to the activity of the virus first isolated in 1933 by Smith, Andrewes and Laidlaw⁽¹⁾ and usually called the virus of epidemic influenza. There are undoubtedly many infections with the clinical appearance of influenza which cannot be shown to be due to influenza virus; but with perhaps one exception (Francis *et alii*⁽²⁾), all large rapidly developing epidemics of influenza which have been studied have proved to be of virus origin. The problem of immunization against influenza is predominantly therefore one of immunization against the virus of epidemic influenza.

As in all such problems, the most profitable lead to a method of artificial immunization is a study of the processes by which the partial natural immunization of communities takes place. Such work has very largely taken the form of observations on the changes in the level of virus-inactivating antibody in human serum in their relation to individual or community experience of influenza. Such observations have been made in large numbers in England, America, Australia and Russia and the conclusions of all workers are in sufficient accord to allow a statement of the position as follows.

In any normal population influenza virus antibody is present in detectable amount in almost all serum, the titre varying greatly from person to person. The average level of antibody is lower before an epidemic than immediately after its passage. All individuals suffering from influenza show a sharp rise of antibody titre in the first ten to fourteen days after infection. A similar though usually smaller rise may be observed in many contacts who show no symptoms of influenza. There is a certain amount of evidence that persons with low initial antibody are more likely to contract influenza during an epidemic than those with a high antibody titre. The difference between the groups is, however, not very striking, and most authors consider that a high antibody titre is to be regarded as an indication of past infection and not necessarily as an indication of a high grade of present resistance to infections.

On the working hypothesis that a raised antibody level would be associated with an increased resistance to infection during an epidemic, most attempts at immunization have followed the conventional lines of subcutaneous injection of living or killed virus. Such procedures have been shown to raise the antibody level; but there is as yet no satisfactory evidence that they give protection against influenza. In ferrets and mice we have found that effective immunity can be produced by the administration of living virus attenuated by chorioallantoic passage and given intranasally (Burnet⁽³⁾). It has previously been suggested that this method may be applicable to the human subject, and a considerable number of inoculations by nasal spray have been given in previous years. With the use of the fully adapted strain "Melbourne" egg, no cases of influenza

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were produced and two small rises in antibody were observed amongst the 30 people tested. No evidence of its effectiveness or otherwise in giving protection against influenza was obtained.

When an opportunity arose of making some tests of immunization procedures in a group of volunteers it was thought that a considerable amount of information might be gained if three consecutive inoculations were given, with strains of progressively increasing virulence, and if serum samples taken before and after the course were studied for changes in antibody titre. In the light of subsequent experience the method adopted could certainly have been improved; but in attempting a new type of procedure with human volunteers, it seemed advisable to keep the methods as simple as possible. The spacing of the injections at intervals of one week instead of longer was partly determined by a factor outside experimental control—the date of a university vacation.

It was thought possible that by the use of such a series of inoculations subclinical infections might be produced in all subjects, the most susceptible acquiring at least a basal immunity from the attenuated first and second strains sufficient for them to withstand the final unmodified strain. This expectation was not fulfilled; but we consider that the experiment provides valuable data on the influence of antibody level on resistance to a standard exposure to infection, and offers useful leads for any further work on the immunization of human beings by infection with living virus. Incidentally it provides evidence of the value of the amniotic inoculation technique in making it possible to use unmodified human influenza virus and to reisolate it from patients with influenza, in both cases without having recourse to ferrets.

Subjects, Materials and Methods.

The subjects of the experiment were 15 university students, aged nineteen to twenty-six years, and two older subjects, aged thirty-nine and forty-one years. None had suffered from clinical influenza during the epidemic of winter 1939, and all were in normal health. The first two instillations of attenuated virus were given in the laboratory and the subjects were merely required to report any symptoms. Since the third instillation was with presumably virulent virus, it was thought necessary that it should be given in strict isolation, and that the subjects should be maintained free from contact with the community for at least seven days thereafter. Through the kindness of Dr. Ivan Maxwell the experimental party was accommodated in a large, well isolated seaside house, and as the experiment was made in August when normal holiday makers were absent, no difficulty was found in maintaining seclusion for the period.

Inoculations were made by spraying the stock virus, diluted 1:5 to 1:10 in saline solution, into the nose and throat with an atomizer. Two pressures of the bulb into each nostril and one to the back of the throat used about 0.25 cubic centimetre of material. In the absence of data at all relevant to the present experiment it was thought advisable to keep the dosage rather low. We can at least be certain that very much more virus was administered than would ever be received in the course of natural exposure to infection, and that each subject received an approximately equal amount under the same environmental conditions.

Blood was taken immediately before the first instillation and again seventeen to twenty days after the final instillation of active virus. Blood was also taken at the time of the illness from each of the subjects who contracted influenza and from two others without symptoms at the same period. The serum was separated, heated for 20 minutes at 56° C., ampouled and stored in a refrigerator. Throat washings were obtained from the patients at the height of fever and were sent at once to the laboratory for filtration and inoculation into chick embryos by the amniotic method (Burnet⁽⁵⁾).

Virus Strains.

1. "Melbourne" Egg. The "Melbourne" egg strain was developed in 1935 and maintained by infrequent passages at intervals of three to six months since; material was

kept in the form of infected membranes in glycerol-Ringer solution at a temperature of about -6° C. during the intervening periods. At the beginning of 1940 it was reisolated by two single pock transfers. The properties of the strain are apparently identical with those described in earlier papers (Burnet⁽⁵⁾). A stock emulsion recently prepared had the following characteristics. The titre on the chorioallantois was 15×10^5 , the embryos dying in two days with typical hæmorrhagic lesions. Mice inoculated with undiluted virus gave lesions, 2, 1, 0, 0, at seven days. Two ferrets, Numbers 126 and 127, showed no symptoms or rise in temperature, but virus could be isolated from filtered nasal washings seven days after inoculation. Ferret 126 gave a serum-producing reduction of pock count to 0.15% under standard conditions—that is, only a weak antibody response. Ferret 127 was proved immune to subsequent test of a virulent strain. In amniotic tests septicæmic infection of the embryo occurred without characteristic lung lesions. The stock virus used in the experiment was prepared by grinding three chorioallantoic membranes and one embryo *minus* beak and limbs to a paste with quartz powder. Two volumes of glycerol-Ringer solution were added to the paste and after light centrifugation the supernatant fluid was stored as stock virus.

2. "Bur." Egg. "Bur." egg was derived from Smith and Andrewes's⁽⁶⁾ "master strain" Bur. by passage on the chorioallantois for 72 generations. It is only incompletely adapted to this situation, producing poor foci and not being lethal for the embryo. In mice it is moderately virulent, a standard egg membrane emulsion killing undiluted and producing lesions to a dilution of 1:1,000. In ferrets it produces no symptoms or fever, but provokes an active antibody response; the result of serum titrations on two ferrets gave values of 0.005% and 0.00075% respectively against "Melbourne" egg virus. In amniotic tests typical lesions are produced and the pooled fluids from infected eggs contain up to 2×10^6 infective units per cubic centimetre. The stock virus was used in the form of pooled amniotic and allantoic fluids mixed with an equal volume of pure glycerol.

3. "Reid, A P I." "Reid, A P I" is the strain R isolated in July, 1939, and described by Burnet and Lush.⁽⁷⁾ Turbinates from ferret 96, which had been inoculated with the original human material, had been preserved in glycerol-Ringer solution and had retained their power to produce infection by the amniotic route. The material used for the third experimental instillation was pooled unglycerolated fluid from eggs inoculated with either the original ferret material or the first amniotic passage. This fluid had a titre of over 2×10^7 infective units per cubic centimetre by amniotic titration. It produced a typical mild response in a ferret, with the initial temperature "spike" rising to 104.3° F., and a subsequent serum titre of 0.0009% against "Melbourne" egg. In mice no lesions or small grade I lesions were produced, and the mice were subsequently fully immune against approximately 100 minimum lethal doses of "Melbourne" mouse strain.

In summary these strains may be described as follows: (i) A fully egg-adapted strain, which had lost most of its specific pneumotropism and had no virulence and only mild immunizing power; (ii) a partially adapted strain, still pneumotropic and mouse-pathogenic, with no virulence for ferrets, but strongly immunizing; (iii) unmodified human virus causing symptoms only in ferrets and in the chick embryo inoculated amniotically.

Isolation of Virus from Throat Washings.

The patients were given 10 cubic centimetres of saline solution to gargle thoroughly. This was then mixed with 5 cubic centimetres of nutrient broth and sent to the laboratory, where it was dealt with the same day. The washings were first passed through sterile filter paper and then through "Gradocol" membranes of average pore diameter 0.8 μ . The filtrates were inoculated into twelve-day chick embryos by the amniotic inoculation technique recently described (Burnet⁽⁵⁾). Usually five eggs were used with each filtrate. Subinoculations from infected embryos were made to further eggs, and further identification of the virus was carried out along orthodox lines.

Serum Titrations.

In view of the occasional discrepancy between serum titrations made by the egg membrane technique and by intranasal inoculation in mice, all serum was titrated by both methods. The tests followed the usual lines, the virus used being egg and mouse strains of "Melbourne". All dilutions were made in cold normal horse serum and saline solution, and mixtures were kept for two hours at refrigerator temperature before inoculation.

Clinical Data.

The inoculations were made on August 2, 9 and 17, with the first, second and third strains respectively. None of the subjects reported any symptoms after the first instillations. Several reported trivial nasal symptoms two to four days after the second instillation. Only in one case ("M.N.") did subsequent serum tests indicate a likelihood that these symptoms were due to infection by the second strain. This subject had a serous nasal discharge, commencing about sixty hours after the inoculation and clearing up within forty-eight hours.

After the third instillation three of the subjects had definite attacks of influenza. The instillations were given at 3 p.m., and the first symptoms were shown by the subject E.L.B. less than twenty-four hours later.

She experienced an irritation of the nose and a desire to sneeze about midday; by the evening her symptoms were those of a typical early cold, with sneezing and profuse serous discharge, but no toxic manifestations and no rise of temperature. On the following morning her temperature was 100.6° F. and she had typical influenzal symptoms, slight shivers, a severe headache, muscular aching, flushed face and running eyes. The subsequent course shown in the temperature chart (Figure I) was that of a mild uncomplicated influenza.

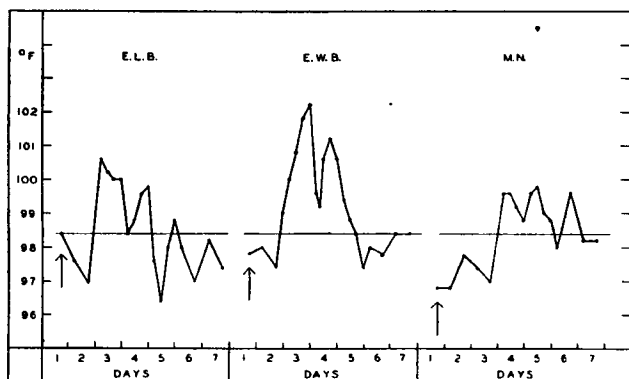


FIGURE I.

Temperature charts of the three subjects who developed clinical influenza. The arrow marks the time of the third instillation of virus.

E.W.B. woke up on August 19 (forty-one hours after inoculation) with frontal headache and slight sore throat. His temperature was 99° F., toxic symptoms increased and the temperature rose steadily to 102.2° F. at 10 p.m. He had a very flushed face and a pulse rate of 120 per minute, and he was obviously ill. At no time did he show any coryzal symptoms. The chart (Figure I) shows the sharply diphasic character of the temperature. Recovery was rapid, but, like E.L.B., he did not feel completely fit again for a fortnight, and lost sixteen pounds in weight.

M.N.'s illness ran a less typical course than the other two. She felt "out of sorts" on August 19 and had some serous nasal discharge. On August 20 (sixty-five hours after inoculation) she had slight shivers and headache, but her temperature was never over 99.6° F. There was some rise of temperature on each of the two subsequent days.

The only other subject to show any rise of temperature was M.S., who had a slight sore throat and a temperature of 99.4° F., fifty-one hours after inoculation. The following morning it was 99.6° F., but she had no general symptoms and her temperature was normal in the afternoon and subsequently. In view of the serological findings she must be regarded as having contracted an influenza virus

infection in which an almost subclinical course was followed.

At the time of the experiment an unusual type of sore throat—"Puckapunyal throat"—was epidemic in Melbourne, and one member of the group, P.R.B., had a typical attack during the last two days of isolation with a temperature reaching 100° F. on August 25. D.C. had a sore throat at the same time and developed a more acute attack on his return home. Washings from his throat on August 28 yielded no influenza virus.

Reisolation of Virus.

Tests for virus in garglings were made by the inoculation of "Gradocol" membrane filtrates into twelve-day chick embryos according to the technique recently described (Burnet⁽⁵⁾). Virus was isolated from all four subjects showing a rise in temperature. In the primary tests the following results were obtained: E.L.B. + (+) (+) (+), E.W.B. + + - - -, M.N. + (+) (+) (+) (+), M.S. + (+) - - -; "+" represents a positive result with typical cells in the tracheal smear, "(+)" a death presumably due to specific infection, and "-" a negative result three, four or five days after inoculation. Typical findings were obtained in all cases on subinoculation from positive primary infections.

One of us has recently suggested a third method of detecting the presence of influenza virus in throat washings (Burnet⁽⁵⁾) based on the fact that unadapted virus in fairly high dilution can immunize mice against virulent mouse virus. Unfortunately the tests were not made immediately the specimens reached the laboratory, but the membrane filtrates and portion of the initial (non-sterile) paper filtrates had been stored in a refrigerator and mice were inoculated about a week later. Fourteen days later a test inoculation of "Melbourne" mouse virus, diluted 1:100, was given. All the mice died with the exception of those receiving filtrates from M.N. Of the four receiving originally the unsterile paper filtrate, three survived with 1, 0, 0, lesions, while one of four given the "Gradocol" membrane filtrate survived with grade I lesions. Since the method requires no filtration apparatus and neither ferrets nor chick embryos, it may be of some practical use and is being further investigated.

With the development of the amniotic method it has been our aim to try to dispense with the necessity for using ferrets at all in influenza virus investigations, and all the strains were identified as influenza virus by the inoculation of mice with infected embryonic fluids and by subsequently testing them for active immunity and obtaining serum for neutralization tests. The details

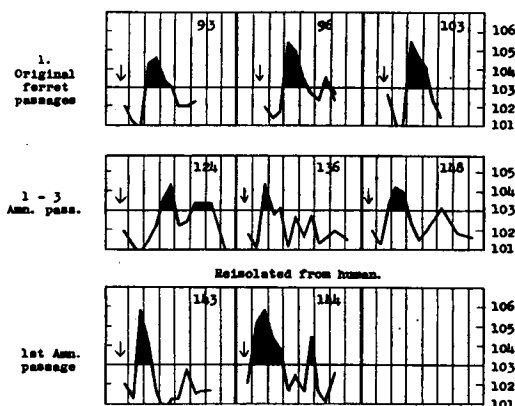


FIGURE II.

A series of temperature charts of ferrets inoculated with the strain R., (i) on first isolation in 1939, (ii) as first or second amniotic passage material prepared in 1940, (iii) as first amniotic passage material after reisolation from E.L.B. (ferret 143) and M.N. (ferret 144).

of this work will be reported later; here it need be said only that all the reisolated strains showed the normal characteristics of a "Melbourne" type influenza virus. Two strains, E.L.B. and M.N., were tested in ferrets.

Both ferrets gave an active response, a rise in temperature above 105°F. , with an unusually short incubation period, in one case less than twenty-four hours, in the other about twenty-eight hours. This response differs quite strikingly from that given by first or second amniotic passage material, such as was used to induce the human infections, and was very similar to that given in ferrets inoculated with material from the original patient "R" (Figure II). This suggests that a certain diminution in virulence had occurred during the year during which the original ferret material had been stored in the refrigerator, but that a single passage through human beings had fully rejuvenated it. It must be recognized that this rejuvenation may have been effective only by increasing the titre obtained in embryonic fluids after inoculation.

Serological Tests.

All the specimens of serum were titrated by the chorio-allantoic method against "Melbourne" egg virus and by the standard mouse intranasal method against "Melbourne" mouse virus. The egg titration results are shown in Figure III, the changes being shown with a reversed logarithmic scale of the percentage of "surviving" foci. The method has been described in several papers (Burnet, Lush and Cade⁽⁹⁾).

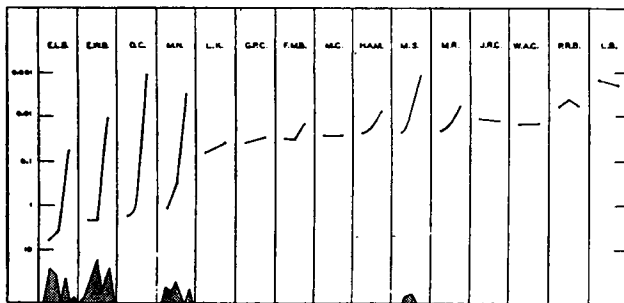


FIGURE III.

Antibody changes as determined by egg membrane titrations. For each subject the preliminary sample of blood was taken before the course of inoculations was begun and the final one two to three weeks after the last inoculation. An intermediate bleeding within four days of the final inoculation was also made in five instances. For convenience of reference a small chart of any febrile reaction after the third instillation is shown under each subject.

The mouse titrations shown in Figure IV are expressed in a similar fashion on the basis of the concentration of virus which, mixed with undiluted serum, will give an average grade II lesion in the inoculated mice. When the serum has to be diluted to give this end point, it is

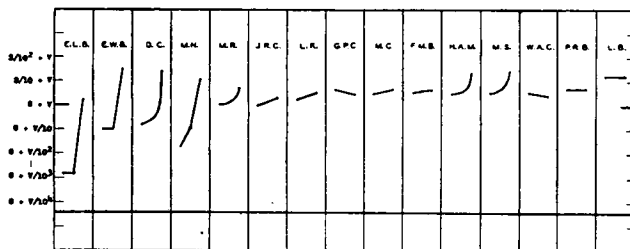


FIGURE IV.

Antibody changes as observed in titrations by intranasal inoculation of mice. The arrangement is similar to Figure III, the points indicating the ratio of serum and virus needed to give rise to average grade II lesions. The scale is logarithmic. The horizontal line gives the dilution of virus which, mixed with saline solution, produces standard grade lesions. S = serum, V = stock virus.

assumed that the same relation holds as has been found with egg membrane titrations, namely, that serum diluted to $1:x$ mixed with undiluted virus would produce the same result as undiluted serum mixed with virus concentrated x times.

It will be seen that there is almost complete concordance in the results obtained by the two methods of testing.

Five subjects were tested for antibody soon after the third instillation of virus, at a time when only the influence of the first and second instillations would be shown. Four, including two influenza patients, E.L.B. and E.W.B., and two who did not show symptoms, P.R.B. and F.M.B., showed no change whatever; the fifth, M.N., showed a definite rise, an approximate tenfold increase in titre from the initial level. This change is clearly visible in both mouse and egg titrations. This is the only evidence from the chart that the first two instillations had any effect whatever. It is possible that they had a significant influence in the case of D.C., but it is probably best to ascribe this and all the other changes shown to the influence of the third instillation of unmodified virus.

On this assumption the most striking feature of the chart is the relationship between susceptibility to clinical infection under the standardized experimental conditions of exposure and the initial antibody level. All three who suffered from influenza had initial antibody below the 1% level by egg titration and the only other subject with a low antibody level showed a very active subclinical antibody response. All the other individuals had relatively high initial antibody levels, and none suffered from influenza, although four showed evidence of subclinical infection by a rise in antibody titre. In the case of one of these, M.S., who showed a sharp rise in antibody, there were minimal symptoms on one day which could reasonably be ascribed to the infection, but which could not be called clinical influenza.

Discussion.

Although so far as its primary object was concerned this experiment was a failure, we consider that it has supplied a good deal of useful information not previously available and has provided a basis for further work on human immunization. In the first place it has provided a clear indication of the value of the amniotic inoculation method for influenza virus research. It has shown that unlimited amounts of high titre sterile virus can be prepared in a convenient form and of any desired degree of virulence. The infections suffered by E.L.B. and E.W.B. were quite similar to the natural cases in the 1939 epidemic from which the virus was derived, and we consider it justifiable to assume that no significant change in the virus had occurred in the interim. Further, the experiment provided the first opportunity to show that virus could be isolated by the amniotic method from human throat washings. The procedure was successful in all instances, including that of the subject M.S., who showed only trivial symptoms. We may note here that subsequently it has been successfully applied in two natural epidemics by Captain G. V. Rudd and ourselves.

In natural epidemics it has been difficult to determine what, if any, influence initial antibody levels have on susceptibility to infection. The present experiment makes it clear that when exposure is standardized the antibody level has a dominant influence in determining the outcome.

With some reservations it seems justifiable to conclude that in susceptible human beings the administration of an amount of unmodified virus enormously greater than would be received in the course of natural infection produces precisely the same clinical effect as the natural infection. The dosage factor seems to be relatively unimportant provided it is sufficient to produce infection.

In retrospect we consider that more information could have been obtained if a longer interval had been allowed to elapse between the second and third instillations and if intermediate blood samples had been taken from all subjects with a low initial antibody level. This would have allowed us to decide (a) whether D.C. was actually immunized by the preliminary instillations, and (b) whether if the commencing antibody response of M.N. had been allowed to develop for a further week she might have withstood the test instillation without symptoms. Despite the doubts about these two cases, there is no doubt at all that neither E.L.B. nor E.W.B. was protected in any way by the preliminary instillations of attenuated virus,

and no evidence that these strains produced infection in them. Susceptible human beings must therefore differ in some essential respect from ferrets and mice in regard to their reaction to attenuated influenza virus. As a working hypothesis we may assume that the most important factor in preventing a "take" of the attenuated strains is the presence of the virus-inactivating agent (V.I.A.) of Burnet, Lush and Jackson⁽¹⁰⁾ in the nasal and (probably) tracheo-bronchial secretions. If this is so, the problem of immunization by living attenuated strains is either to select a strain resistant to V.I.A. or to restrict the output of V.I.A. temporarily by some pharmacological manoeuvre to give an opportunity for infection to be initiated.

We feel that the control of influenza by immunological means will never be a practicable proposition unless the immunizing agent is capable of being prepared rapidly and in very large amount and can be administered easily to very large numbers of people. Only egg-grown viruses administered by the natural route seem to offer at present the required potentialities, and despite the failure of our present attempt we hope to be able to continue work along these lines.

Summary.

1. A group of 15 volunteers received inoculations into the nose and throat of three strains of influenza virus of progressively increasing virulence.
2. Three subjects suffered from clinical influenza following the instillation of virus, which was considered to be of full human virulence.
3. Serological results from all subjects are shown in graphs. They indicate the high correlation of resistance to a standardized exposure, with high antibody level.
4. The attenuated strains administered appeared to have no significant protective effect.
5. Virus was readily reisolated from all subjects showing clinical symptoms by the inoculation of throat-washing filtrates into chick embryos by the amniotic route.

Acknowledgements.

This experiment was made possible only by the helpful cooperation of many individuals. We are especially grateful to Dr. Ivan Maxwell and Mrs. Maxwell for providing an ideal setting for the experiment at Dromana and for assistance in many practical details. Dr. C. H. Kellaway was largely responsible for the initiation of the experiment, and we are indebted to him not only for the bulk of the organization, but also for much useful criticism of methods and results. The fact that most of the volunteers spent a very pleasant holiday was largely due to the work of Mrs. N. Hamilton Fairley, Mrs. P. Whitehead and Miss L. Shaw, who undertook the provisioning, house-keeping and nursing required during the period of isolation. Finally we have to thank our subjects for their cooperation and interest. They were: Mrs. F. M. Burnet, Miss L. Barr, Miss M. Cunningham, Miss L. Keipert, Miss M. Nash, Miss M. Ross and Miss M. Shelton, and Mr. E. W. Bate, Mr. P. R. Bull, Mr. J. R. Collie, Mr. W. A. Cooper, Mr. D. H. Cowling, Mr. G. P. Cromie and Mr. H. A. Marks.

References.

- (1) W. Smith, C. H. Andrewes and P. P. Laidlaw: "A Virus Obtained from Influenza Patients", *The Lancet*, Volume II, July 8, 1933, page 66.
- (2) T. Francis, Junior, T. P. Magill, E. R. Rickard and M. D. Beek: "Etiological and Serological Studies in Epidemic Influenza", *The American Journal of Public Health*, Volume XXVII, Number 11, 1937, page 1141.
- (3) F. M. Burnet: "Influenza Virus on the Developing Egg. 4. The Pathogenicity and Immunizing Power of Egg Virus for Ferrets and Mice", *The British Journal of Experimental Pathology*, Volume XVIII, 1937, page 37.
- (4) F. M. Burnet: "Influenza Virus Infections of the Chick Embryo Lung", *The British Journal of Experimental Pathology*, Volume XXI, 1940, page 147.
- (5) F. M. Burnet: "Influenza Virus on the Developing Egg. 1. Changes Associated with the Development of an Egg-Passage Strain of Virus", *The British Journal of Experimental Pathology*, Volume XVII, 1936, page 282.

(6) W. Smith and C. H. Andrewes: "Serological Races of Influenza Virus", *The British Journal of Experimental Pathology*, Volume XIX, 1938, page 293.

(7) F. M. Burnet and D. Lush: "Influenza Virus Strains Isolated from the Melbourne 1939 Epidemic", *The Australian Journal of Experimental Biology and Medical Science*, Volume XVIII, 1940, page 49.

(8) F. M. Burnet: "Influenza Virus Infections on the Chick Embryo by the Amniotic Route. I. General Character of the Infections", *The Australian Journal of Experimental Biology and Medical Science* (in the press).

(9) F. M. Burnet, J. F. J. Cade and D. Lush: "The Serological Response to Influenza Virus Infection During an Epidemic, with Particular Reference to Subclinical Infection", *The Medical Journal of Australia*, Volume I, March 23, 1940, page 397.

(10) F. M. Burnet, D. Lush and A. V. Jackson: "A Virus-Inactivating Agent from Human Nasal Secretion", *The British Journal of Experimental Pathology*, Volume XX, 1939, page 377.

SOME ASSOCIATIONS OF THE OLD HOBART GENERAL HOSPITAL.¹

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Hobart.

I. YESTERDAY.

THESE few memories of the old General Hospital are prompted by its recent demolition and the erection on its site of the Royal Hobart Hospital. They are based on my own experiences and on chance remarks made from time to time by my father (E. L. Crowther, M.D.). At the opening of this century he had been for many years one of the honorary staff. It was his custom to visit his patients there late on Sunday afternoon as well as on his ordinary ward days. By walking there and back with him and using my eyes during the long wait in the hospital grounds, I am able to take my early memories back for some forty-five years. As a student and resident medical officer and now as a member of the honorary staff, my association with the hospital has continued with occasional breaks ever since.

In the late nineties the hospital, built in 1841-1842 as Her Majesty's Colonial Hospital and in later years known as the General Hospital, housed male patients of all ages (Figure I). The newer stone two-storey building, overlooking the Hobart rivulet in the back of the grounds, was the female block. There was no children's hospital, nor was any ward set apart for them; children were treated in the male or female wards. The site of the present children's hospital was then occupied by several small shops and the Union Hotel. This very old two-storey structure was the one in which, tradition has it, Lieutenant-Governor Davey spent much of his time when the formalities of his office were too much for him. Entrance to the hospital was through iron gates between two lodges each of cut freestone with slate roofs; they were given over to day and night porters respectively. Inside each was a small room with cedar cupboards flanking a mantel of the same wood. During the winter a generous coke fire was kept going, and here their cronies gathered in the evenings. There was no telephone from the gates, and the porter, having admitted the patient, took him or her to the casualty room and then set off in search of the resident medical officer or sister to be notified of the emergency. In later years the porters were given first a bell extension and eventually a telephone. Their hours were from 8 a.m. to 8 p.m. for day duty and from 8 p.m. to 8 a.m. at night. The two whom I remember best, named Nagles and Scurrah, wore a blue uniform with a peaked cap carrying the imperial crown. Just opposite the hospital gates lived Mr. Woods, the cabman, who was called on for transport in all emergencies. If I remember rightly, he drove at that time a black conveyance, the equivalent of the modern ambulance. Across the street was the old police station (Figure II), which many years earlier had served to house in part the female patients of the hospital. The old hospital, just demolished, of two storeys with attics, was faithfully built of an unexcelled

¹ Read at a meeting of the Tasmanian Branch of the British Medical Association on May 14, 1940, at Hobart.