Whether or no this proves to be the true explanation, the interpretation of the failure of the kidney in certain stages and cases of nephritis to show any morning alkaline tide still requires investigation; this is being prosecuted. But in the cases available for the work of which this is a preliminary report it is not a failure of the kidney in its power to turn out acid that is indicated; the abnormality is that the kidney gives an acid urine in conditions in which a normal kidney gives an alkaline urine. The question arises, therefore, whether this abnormality may not be an expression of an effect of the disease of the kidney on the function of some other organ. The gradual return to the normal type of response shown in tests done on the same patient at intervals of two or three weeks during recovery is striking, and in a fuller account of the work to appear later will be illustrated by protocols.

NOTES ON THE INFLUENZA EPIDEMIC IN THE EGYPTIAN EXPEDITIONARY FORCE.

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Epidemiology.

THE epidemic in this force commenced in May, 1918, but the maximum incidence was not reached till September and October. The cases during the earlier period of the epidemic were on the whole mild in type and of short duration, only a very small proportion being complicated by bronchopneumonia.

Patients already debilitated by malignant tertian malaria influenza proved much more serious, many developed bronchopneumonia, and considerably over 50 per cent. of such cases ended fatally.

The epidemic continued throughout November, December, 1918, January and February, 1919, but the number of cases showed a marked decrease during the last two months. In the latter part of the epidemic few of the cases were complicated by malaria, and one had a better opportunity of studying the disease in otherwise healthy individuals. The type of the disease also changed somewhat towards the end of December, and showed on the whole a tendency to become less virulent; this feature has been maintained up to the present time.

As regards the incubation period, but little evidence is available, for the sources of infection were so general that it was rarely possible to determine the original focus in any given case. There are many features with regard to the infectivity of this epidemic which call for comment; for, while in the early influenzal stage the disease seems to be markedly infectious, yet directly bronchopneumonia supervenes its infectivity appears to be much diminished or lost altogether. This point is supported by the fact that hardly any of the sisters, medical officers, or orderlies in close contact with bronchopneumonic cases have contracted the disease.

Clinical Types.

The cases can be divided into three more or less well defined groups:

1. Catarrhal type.
2. Bronchopneumonic type.
3. Toxaemic type.

A large proportion give a history of a severe cold preceding the acute febrile period by a few days. Otherwise the onset of the disease proper is sudden, being marked notably by fever, headache, pains in the back and limbs, and lassitude. The more severe attacks were often ushered in by vomiting. The headache is generally frontal, and associated with pain in the eyes. I shall now describe the types of cases more in detail.

TYPE I: Catarrhal.—The febrile period usually extended from five to seven days, the maximum temperature being reached on the second day. It rarely exceeded 103° F., though in a few cases temperatures of 104° F. and over were met with. The temperature usually fell by lysis, though in a few cases, more especially in those treated with vaccine, the fall was more rapid. The pulse rate was increased, but rarely exceeded 116

to 120, whilst the respiration rate showed but little change. Tracheitis and pharyngitis were common, and associated with these was a dry and troublesome cough, with little or no secretion. No gastro-intestinal symptoms were present, except those usually associated with febrile disturbance—that is, furred tongue, loss of appetite, and constipation. After the subsidence of the fever the patients rapidly regained their normal strength, and post-influenzal debility was not a marked feature.

TYPE II: Bronchopneumonic.—During the early stages of the disease there was no means of distinguishing between Types I and II, except on the whole the onset in the latter type was liable to be more severe and the fever during the initial stages to be at a higher level. Usually it was not till the third or fourth day of the disease that one could classify any given case, when the temperature, instead of falling, would remain at the same or at a higher level, and the patient would be much more distressed. At the same time the pulse and respiration rates would show a greater deviation from the normal. Pain in the chest was a prominent feature, though physical signs at this stage would be absent, and they rarely appeared before the fourth or fifth day of the disease. The earliest signs usually detected were some fine sticky crepitations heard at the end of inspiration over one or both bases. A peculiar characteristic of these crepitations was that often they could only be heard once or twice during a single examination and would then disappear altogether. Once physical signs had appeared they became rapidly intensified with obvious crepitations, râles, and accentuation of vocal resonance. As compared with the slight physical signs during life, the striking feature *post mortem* was the wide extent of the pulmonary lesions. The sputum was at first very scanty, glutinous, and streaked with blood. "Rusty sputum" was rare. In the later stages, especially in those recovering, the sputum became abundant and purulent. After the development of bronchopneumonia the course varied, all grades of severity being met with. On the whole the course of cases with a severe onset, associated with vomiting, and those with high fever during the initial stages, was more severe and the prognosis correspondingly graver. There was a marked tendency for the bronchopneumonic process to spread throughout the lung, and perhaps affect the opposite side in similar fashion, so that during the course of the disease practically the whole lung tissue would become involved in the morbid process. Fortunately, in cases of this type, the portion of the lung first affected would rapidly resolve and be functional when other portions were being attacked. Many cases of this type recovered. Pleurisy occurred in a fair proportion of cases, but usually after the temperature had begun to subside. Its intervention did not appear to render the outlook more grave. Cases were seen in which during the early stages tracheitis was absent, but who, at a later date, developed bronchopneumonia, so that tracheitis does not appear to be an essential forerunner of the bronchopneumonic type.

TYPE III: Toxaemic.—This type is characterized by acute and severe onset, nearly always accompanied by vomiting, high fever, rapid pulse and respiration. The patient is flushed and anxious-looking, and obviously acutely ill from the commencement. The duration of this type is from two to five days, and they die usually exhibiting more a clinical picture of acute toxaemia than that of bronchopneumonia. In one case death supervened eight hours after the onset. During the later stages the flushing is replaced by a peculiar lilac coloured cyanosis affecting the face and neck, but most marked over the lips and ears. This feature is frequently seen in severe cases of the second type, and once it has set in the prognosis is practically hopeless. Death usually supervenes within forty-eight hours. Apart from a general erythema and herpes, no rashes have been seen. Cerebral symptoms have not been commonly met with, and consciousness is retained almost to the end. Subclitus tendinum, with twitching movements of the hands and arms, have frequently been observed. Delirium was common during the earlier phases of the epidemic, but practically disappeared towards the end. It will be seen that the line of demarcation between the first and second types is by no means well defined.

I have detailed the clinical features of this epidemic in order to establish its identity with that encountered elsewhere as forming part of the pandemic, for when we come to study the bacteriology several points are found at marked variance with those of other observers.

Bacteriology and Vaccine Treatment.

Owing to the prevalence of other diseases requiring laboratory assistance for their diagnosis, but little bacteriological work could be done on influenza during the early phases of the epidemic, and consequently one could not concentrate on it until it had assumed a much more serious aspect. The primary work consisted solely of the examination of sputa from all types of the disease, and the preparation of autogenous vaccines for some few of the serious cases which showed a tendency to become chronic. During the course of these examinations it was observed that a Gram-positive strepto-diplococcus was almost constantly present—thus out of 300 sputa examined it was present in 95 per cent., and very commonly it was the predominant organism, so much so that cultures on suitable media would yield an almost pure growth.

From *post-mortem* specimens of lung this organism was again found in large numbers, sometimes alone and sometimes associated with a pneumococcus. The strepto-diplococcus was also found in the liver, spleen, heart's blood and kidney *post mortem*, and in the aspirated pleural effusions during life. It was also found in a subcutaneous abscess occurring in the course of the disease, in two cases, unassociated with any other organism. One fatal case,* which occurred recently, was complicated by surgical emphysema, and the strepto-diplococcus was obtained in pure culture immediately after death from the subcutaneous tissues affected.

Morphologically this strepto-diplococcus is identical with one found commonly in the nasopharynx of normal individuals, or in those with some mild catarrhal condition of the mucous membrane. Later, blood cultures were carried out in forty cases at all stages of the disease. In three the strepto-diplococcus was isolated, whilst in one other a diphtheroid organism was obtained. The last case was moribund when cultured, and the infection with the diphtheroid may be regarded as a terminal one. As regards the former, two of these cases were of the acute toxic type, and the blood culture was performed on the second day of the disease; one of these died forty-eight hours and the other seventy-two hours later. The third* case from whose blood the strepto-diplococcus was isolated belonged to the second type, and eventually made a good recovery.

From these facts it was obvious that, whether one regards this strepto-diplococcus as the primary cause of the disease or not, it was certainly responsible for a very large proportion of the fatalities. For this reason, together with the very encouraging results achieved in the more chronic cases by the autogenous vaccine treatment—a vaccine composed of morphologically identical organisms—I ventured to suggest that a polyvalent stock vaccine should be given, tentatively at any rate, to a larger series of cases.

The first batch of stock vaccine used was prepared from strains isolated from sputa and lungs at autopsy; to this was added a third of pneumococcal emulsion also derived from lungs. Towards the end of October, 1918, vaccine treatment was commenced, and the preliminary results obtained in the early series of 20 cases was most encouraging. There were two deaths, one of which was complicated by acute bacillary dysentery, whilst the other was found *post mortem* to have suffered from military tuberculosis. Tabulated in this manner they gave the following results:

Number of cases	...	...	...	20
Deaths	...	...	...	2
Recoveries	...	...	...	18
Mortality	...	...	...	10 %

Cases treated on symptomatic lines during the same period at the same hospital gave the following results:

Number of cases	...	...	...	43
Deaths	...	...	...	15
Recoveries	...	...	...	28
Mortality	...	...	...	35 %

Whilst fully acknowledging that statistics derived from such a comparatively limited series are liable to be misleading, it is necessary for me to emphasize that this line of treatment was carried out on Indian soldiers without any selection being made. It was made a routine that every third case diagnosed in the pneumonia ward and belonging to my second type received vaccine treatment.

Before commencing treatment smears of the sputum were examined to determine the presence of the strepto-diplococcus. The scheme of dosage employed in these early cases was as follows:

Initial dose	...	...	5,000,000
Interval 48 hours.	...	...	
Second dose	...	...	10,000,000
Interval 48 hours.	...	...	
Third dose	...	...	15,000,000
Interval 72 hours.	...	...	
Fourth dose	...	...	20,000,000

This scheme had to be modified occasionally. No marked reactions or untoward symptoms manifested themselves as a result, but on the contrary the patient usually improved clinically shortly after the commencement of treatment. I wish especially to call attention to the definite drop in temperature which took place after each

injection. These results appeared to me to justify a much wider application of the vaccine treatment, and it was therefore provided to the casualty clearing stations and stationary hospitals in the district in which I was working.

Although for obvious reasons it has been impossible to keep accurate statistics throughout the epidemic, nevertheless all the medical officers who have been employing the vaccine have reported favourably upon it. Within the last two months the scheme of dosage has been modified, the initial one being increased to 10,000,000 cocci, to be followed after an interval of forty-eight hours by 20,000,000. Further increases are of 10,000,000 per dose. Provided that no untoward symptoms are observed, the intervals as described in the first scheme should be observed.

Much larger doses have been given without any untoward results. One medical officer reported that he had administered 50,000,000 to an apparently moribund Egyptian patient, who ultimately recovered. Other cases seemed to indicate that still better results might be obtained with a higher dosage. It has only been in a minority of cases that the vaccine does not appear to influence the course of the disease; but it is without value in the acute toxæmic forms.

In order to obtain the best results vaccine treatment must be instituted as early as possible, and I have strongly advocated its use in the early catarrhal stage. That this view has some justification is shown by the fact that a much smaller proportion of cases thus treated proceed to the bronchopneumonic stage.

The physical signs of pulmonary complication do not usually appear till the fourth or fifth day of the disease, so that vaccine treatment should not be delayed till these signs appear; the essential point, to my mind, is to immunize the patient against the strepto-diplococcus before actual consolidation has taken place, for when audible signs are present it indicates that considerable pathological changes are already present in the lung, and it may be too late to produce an effective immunity. Severe cases and those tending to become chronic should be treated with an autogenous vaccine, the stock vaccine being reserved for primary usage, pending the preparation of an autogenous one.

It is advisable to examine Gram-stained films for the strepto-diplococcus in all cases where vaccine treatment is contemplated and sputum is available, for in a small minority it plays little or no part in the pathological process.

Morphology and Cultural Characteristics of the Strepto-diplococcus.

Sputa examined from early cases of the disease show large numbers of Gram-positive, non-capsulated diplococci, arranged in chains of varying length, composed of four to twenty or even more cocci. In fresh specimens and young cultures the organism is uniformly Gram-fast, but in older sputa and cultures, as well as smears obtained from the tissues, the diplococci are liable to lose their staining properties. In addition to Gram, it stains well by all simple stains. The size of the organism and the length of the chain it forms vary somewhat in culture on different media, but this strepto-diplococcal arrangement is a constant feature. Involution forms are common, especially on solid media.

The organism is easily isolated from sputa by plating on plasma-glucose-agar, and it is possible to obtain an almost pure primary plate from fresh sputa in early cases. The colonies are small, grey, translucent, circular in outline, and rather flat-topped. It grows poorly on ordinary media, but freely on those containing glucose, with plasma or serum. Unless subcultured every twenty-four hours it rapidly dies out, and even then it is most difficult to keep it alive for more than six or seven days at a time, for each subsequent subculture gives a less vigorous growth. The best medium for this purpose is apparently 1 per cent. glucose-serum broth.

The reaction of twenty strains corresponding morphologically to this description has been tested against the following sugars and alcohols; in the main the reactions are constant, though differences in the degree of acidity are sometimes marked.

Glucose	...	...	Acid	Dulcitol	...	...	Acid
Lactose	...	...	0	Mannite	...	...	0
Maltose	...	...	0	Milk	...	...	Acid and clot
Saccharose	...	...	Acid				

On the whole strains isolated from blood and pleural effusions produce more strongly marked reactions than those isolated from sputa. Thus little or no clot production in milk was observed in strains isolated from sputum, though this was a marked feature in strains isolated from other fluids. All strains were markedly haemolytic.

The strepto-diplococcus proved to be non-pathogenic to all the available laboratory animals, guinea-pigs, rats, and rabbits.

* Both these cases were investigated by my colleague, Captain J. Anderson, R.A.M.C. The latter was treated with intravenous injections of eusol.

One of the most notable bacteriological differences between the epidemic occurring in Egypt and Palestine and in Europe has been the almost complete absence of bacilli corresponding to the Pfeiffer type. During examination of film preparations of sputa at all stages of the disease, Gram-negative micro-bacilli of Pfeiffer type were only observed in twelve cases, and in three cases only has anything corresponding to the *Bacillus influenzae* been isolated in culture, although media recommended by observers in England as specially suitable for the isolation of this micro-organism, including that of Matthews,¹ and the "K" medium quoted by Fildes, Baker, and Thompson, have been repeatedly used. I find also on inquiry that these results as regards the almost complete absence of *B. influenzae* correspond with those of other laboratory workers in the district.

Many *post-mortem* examinations have been made, but as results coincide with those detailed by other observers, they have been omitted from this article. In this connexion I would like to thank Major P. H. Bahr, D.S.O., R.A.M.C., for his assistance and many valuable suggestions.

CONCLUSIONS.

1. There is no valid reason for assuming that the primary cause of influenza in Egypt and Palestine differs from that of the recent pandemic.

2. There is no justification for regarding *Bacillus influenzae* (Pfeiffer) as the primary cause.

3. From the work of various investigators, it is more reasonable to regard both the influenza bacillus and the strepto-diplococcus as secondary invaders, the former being the predominant organism in Europe, the latter in Egypt and Palestine.

4. In this case it is more than possible that the primary etiological agent is ultramicroscopic and is a filtrable virus, which renders the individuals infected hypersensitive to organisms which formerly only possessed a low degree of pathogenicity.

It is hoped that the favourable results achieved by the vaccine treatment will dissipate—in part, at any rate—the diffidence felt by many medical men to the employment of vaccine in acute pulmonary cases and will stimulate further investigations on this branch of therapeutic bacteriology. Work is now being conducted with a view to producing an antiserum in horses to this strepto-diplococcus.

REFERENCES.

- ¹ Abrahams, Hallows, and French: *Lancet*, January 4th, 1919.
² Matthews: *Ibid.*, July 27th, 1918. ³ Fildes, Baker, and Thompson: *Ibid.*, November 23rd, 1918. See also W. F. T. Haultain, *BRITISH MEDICAL JOURNAL*, April 26th, 1919, p. 517.

AN ADDRESS ON GOITRE.*

BY

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It is a very difficult thing for a man in an ordinary country practice to write a paper that would interest any number of the medical profession. He is in a totally different position from the surgeon, the consulting physician, or the bacteriologist. If he meets with a very interesting case—occasionally he does—he rarely if ever has anyone to consult, nor can he compare notes with any other practitioner.

A disease the frequency of which has been puzzling me for some time in a portion of my neighbourhood is goitre, and I thought an account of a few facts I have noted might not be inopportune on this occasion. I do not claim to have discovered anything new either in cause or treatment, but I think there are some differences between the symptoms in the majority of the cases I have met with and what I have seen described in books, notably in the time of onset and the proportion of males and females affected.

In July, 1918, there was a garden party at Hillsborough for the purpose of raising funds for a neighbouring church, and a number of young women from a district, to which I shall refer later, were present. In the evening I happened to have a good view of them as I occupied a seat on a

platform facing the audience. In the front row there were twenty-two young women, and out of these I counted sixteen with enlarged necks. I drew the attention of three persons who were sitting beside me to what I had observed, and asked them to tell me how many they thought were affected. They all arrived at about the same number.

I do not, however, wish it to be believed that anything like 70 per cent. of the young women are affected, but on this particular occasion they happened to be congregated.

Twenty or twenty-five years ago goitre was almost unknown in this district, but at the present time I know of and have seen between sixty and seventy cases. It is quite possible there may be a few more, as I am rarely consulted about it unless there arises some difficulty in breathing or swallowing. All the cases, with one exception, are of the female sex, and in over one half the right side of the gland is larger than the left. In no case have I seen the left larger, whilst, in the only male case that I know, the left is the side most affected. Why the left side should be larger in the male and the right in the female is an interesting problem; it seems to indicate that sex plays an important part in the susceptibility of different lobes of the thyroid to disease.

The gland in most cases begins to enlarge when the girls are about thirteen or fourteen. Now Dr. McCarrison in his book says that school children are more susceptible than adults when they are subjected to goitrogenous influences, and that the most susceptible age is 9 in the case of boys, and 10 in the case of girls, and that up to the age of puberty both sexes are affected equally. I do not know of a single child attending school showing any symptoms of the disease. I have spoken to several national school teachers on the subject, and in no case have they noticed a swelling or prominence in the necks of any of the scholars. The majority of children leave these schools when they are about thirteen or fourteen years of age.

Dr. McCarrison also says that in the localities where goitre is not supposed to be endemic the thyroid enlarges during pregnancy in nearly half the cases. I know of two cases that developed in the past year during pregnancy. The enlargement was first noticed by the patients about the fifth or sixth month. In one of these cases the enlargement was much the same when I saw it last, about four or five months after the child was born. In the other it had decreased; she has a sister with a fairly large goitre of sixteen years' standing, and their mother informs me that she herself had one which disappeared about twenty-two years ago, shortly after her last baby was born.

I see from several books I have consulted that defective or improper food, insanitary dwellings, bacterial and other toxins, infectious diseases, constipation and intestinal stasis, fright, mental worry, consanguinity, and heredity, are all given as exciting causes.

The majority of these causes are out of the question in this locality. There is not much wrong with the food; the people are as well fed—better, I believe—than ever they were. The dwellings are far more sanitary than they were thirty years ago—the old mud walls, thatched roofs, earthen floors, and small windows that did not open, are things of the past; and the filthy cesspools and stagnant water holes have almost disappeared. There had been no serious epidemics before the late outbreaks of influenza. Intestinal toxæmia is, I suppose, much as ever it was, while constipation is not a common condition in girls of 13 or 14.

The water supply in the labourers' cottages built by the rural council is different. Before these cottages were built shallow wells, from which the water could be lifted with a can, supplied the drinking water. Now a deeper well, with a pump, is the rule, and it is quite possible that the water now used is not the water originally supplied, but comes from some distant and polluted source. We have a few cases in the village of Hillsborough where the water supply is almost the same as it was forty years ago. The majority of the people are supplied from pumps. I have had the water from these analysed at various times, and several of the samples were certified to be contaminated with sewage.

The district in which the disease is most prevalent, and where the girls I saw in Hillsborough came from, lies along the banks of the Lagan Navigation Canal and the river Lagan. It is low lying, from 110 to 150 feet above sea level, and is bounded on the north and south by fairly

* Delivered at the annual meeting of the Belfast Division, June, 1919.