toxin which acts as an immunizing agent, being favourably placed for acting in this way.

The process of exposure to the sun must be gradual or a dangerous reaction may be set up; the explanation of this is, I think, that the destruction of a large number of cells, before immunity to the toxin has been set up, results in the formation of an excess of the same toxin that is already producing the symptoms of the disease, in the same way that an overdose of a vaccine is followed by a severe reaction.

It is impossible to believe that the rays of the sun can have such powers of penetration as to have any direct bactericidal effect on tubercle bacilli deeply situated in a gland or bone. The explanation that I have suggested seems to me to be more probable, and certainly more tangible, than that given by Dr. Rosselet in Professor Rollier's book on heliotherapy:

"The energy given out by the radiations is stored and carried in the blood stream to every part of the body; when liberated it stimulates the intracellular processes of oxidation and reduction."

In this connexion it is of particular interest to note that guinea-pigs inoculated with haematoporphyrin acquire an extraordinary hypersensitiveness to sunlight and ultra-violet rays. I do not know what explanation of the phenomenon has been given, but I believe that it may be regarded as an anaphylactic reaction, the haematoporphyrin (a derivative of red blood cells) sensitizing these animals so that a subsequent dose of a similar or closely allied substance, liberated by the destructive action of sunlight on red cells, rapidly produces toxic symptoms.

SUMMARY.

It is well known that the red corpuscles of animals of one species are toxic to animals of another species; Vedder⁶ has shown that human red-cell stroma, freed from haemoglobin, is exceedingly toxic to rabbits. In this communication an attempt has been made to show that the stroma of human red cells, when disintegrated by heat or by mechanical means, is toxic to the individual from whom the blood was withdrawn and to other individuals; it is also shown that many bacteria have a disintegrative effect on red cells. It is inferred therefrom that this endocellular toxin is a factor in causing the manifestations of bacterial infections, and a method of treatment is suggested based on these deductions and aiming at immunizing the body against this toxin.

The toxin produced by the destruction of red cells is probably an example of a "poison of metabolic origin," such as gastrototoxin, hepatotoxin, etc., though in most cases these toxins have been produced by the injection of the particular cells of one animal into another of a different species. C. Bolton⁷ produced an isogastrototoxin by immunizing the rabbit with the gastric cells of a rabbit, and Ehrlich⁸ has shown that an isohaemolysin might be formed in the goat by the injection of goat's blood which would dissolve the blood of another goat. I am not aware that it has been previously shown that human disintegrated red cells are toxic to the same and other individuals.

Reference must be made to a paper by S. G. Billington,⁹ in which he describes how certain "coccoid bodies" are formed from the red cells when a few drops of blood are added to a tube of distilled water with 0.5 per cent. ammonium carbonate and heated to 58° C. These coccoid bodies he regards as possibly allied to or identical with micro-organisms, and he has treated a large number of bacterial infections with vaccines prepared from these bodies. I have found that the debris resulting from heating washed red cells in the way I have described consists, microscopically, of similar "coccoid bodies"; if the medium is normal saline the spheres are large—about a quarter the size of red cells—while if weaker saline, or distilled water, is used they are smaller and have the appearance and often the arrangement (pairs, short chains, etc.) of cocci. Their staining reactions, however, are these red cells.

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SOME NOTES ON EPIDEMIC ENCEPHALITIS.*

BY

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It is not my intention to attempt to give anything like a complete account of the cases of epidemic encephalitis admitted to the fever hospitals under my care during the very sudden and extensive epidemic in Belfast during the spring and early summer of 1924. I shall merely endeavour to refer to some of the outstanding features of that outbreak, and to give some notes and figures gleaned from my experience of that very large number of cases.

The outbreak began at the end of March, 1924. For the first three weeks the cases were few; about the middle of April there was a sudden large increase in admissions, and cases continued to come in large numbers until the end of June, when the epidemic ceased even more suddenly than it began. This seasonal outbreak coincides exactly with our experience in 1920, the only other year in which there has been any extensive epidemic in Belfast. The total number of cases admitted to the fever hospitals in the outbreak of 1924 was 183.

Differences in the type of attack in the cases in this recent outbreak, compared with the earlier epidemics, have been noted everywhere, but I think much, though not all, of this difference is more apparent than real. The descriptions of the signs and symptoms in the early stages of the disease which have appeared in medical literature are necessarily to a large extent based on observations made on cases after their admission to hospital. Whereas in the earlier outbreaks cases very rarely reached the hospitals until lethargic symptoms had developed, in this epidemic the cases were much more quickly diagnosed, and were frequently sent to hospital in the stage of excitement and insomnia. This naturally left with the hospital physicians a very different picture of the early signs. I know that, speaking for myself, I did not fully recognize until the outbreak of 1924 the very great diagnostic value of a history of persistent insomnia, mental excitement, and talkativeness at the onset.

SYMPTOMS.

The prominent symptoms at the onset of this outbreak were: (1) Fleeting superficial neuralgic pains; (2) nocturnal insomnia, often complete and lasting for several nights; (3) mental excitement and exaltation, great restlessness and talkativeness; a little later came (4) diplopia and other eye signs; (5) muscular twitchings of varying degree; (6) delirium of varying degree; and later still (7) lethargy of varying degree. It is, of course, true that in many cases some of these symptoms were entirely absent.

1. *Neuralgic pains* were reported in the large majority. Common sites were: the scalp; over the ears and sides of neck, often extending over the shoulder and arm; the forearm; the fingers, especially the thumb; over the iliac crests, one or both; occasionally pains in the leg or foot were present at the onset, but more commonly this was a later, and often very troublesome, manifestation. In a few cases the first symptom was pain high up in the axillae, and in some very acute pain in the perineum. In many cases if the painful part were firmly handled the pain was slight or absent, but light touching or stroking was intensely painful.

2. *Nocturnal insomnia* was present in a large majority as a very early sign. Many patients were unable to sleep at all for four, six, or even eight nights.

3. *Mental excitement, restlessness, and talkativeness* were very common at the onset; the talkativeness was particularly striking in many cases seen in the very early stage. In many there was a history that if left alone the patient whistled or sang all through the night; and more than one patient after admission to hospital treated the ward to a continuous vocal concert throughout the night.

* Abstract of a paper read before the Ulster Medical Society on

4. *Diplopia and other Eye Signs.*—Diplopia was present in 73 per cent. of my cases; generally it was not observed until the second or third day. In some it was the first symptom complained of, but in most of these cases careful inquiry elicited a history of previous wakefulness and restlessness. Squint, nystagmus, and partial loss of accommodation were frequent. Conjunctivitis was noted in only a small proportion.

5. *Muscular Twitchings.*—Here I think there was a marked difference between the recent cases and those seen in former outbreaks. Twitchings, myoclonic jerks, and general choreiform movements were much more commonly seen in this outbreak. They were present to some degree in over 70 per cent. of my cases. In many the jerkings were mild, confined to the limbs, with, in some, twitchings in the lips, tongue, and eyelids; in these they generally passed off in a few days. In many they were very severe and persisted for weeks or even months. In several the patients looked, at first sight, like severe cases of chorea. In these the skin over all prominent parts was often greatly excoriated from rubbing on the bed and clothes. Myoclonic jerkings of the abdominal muscles were common, with or without pain, and often slow in clearing up. In one very severe case the abdominal jerks were still present, at the rate of twenty to the minute, at the end of five months.

6. *Delirium* was noted in 52 per cent.; it varied in degree from slight nocturnal mutterings to severe maniacal states somewhat resembling delirium tremens. In several instances it was necessary to sheet the patient down in bed. Hallucinations were noted in several cases.

7. *Lethargy* was present at some stage in 72 per cent.; it varied greatly in degree. Generally it appeared in the third or fourth week. In many it was at first only in the daytime; the patient continued wakeful at night. Later it was continuous. In a few cases there was profound coma lasting for weeks, necessitating nasal feeding, etc. In a few lethargy was the first sign observed.

Herpes was noted in 6 per cent., generally on the lips or nostrils, but occasionally at other sites.

Respiratory Disturbances.—Attacks of polypnoea were common both in early and late stages. Many showed sudden attacks of very rapid shallow breathing (60, 80, or 100 a minute) lasting from a few minutes to hours, especially during sleep, and often accompanied by panting.

Polyuria was common. One patient, a woman of 48 with a very severe attack, was at the twelfth week passing 500 to 600 ounces of urine a day, with a specific gravity down to 1002. This rapidly became normal after lumbar puncture.

Cerebro-spinal Fluid.—Lumbar puncture was made in many cases. Little that varied from the normal was found except an increased sugar content. This increase in the sugar is a valuable diagnostic sign, especially in differentiating from meningitis. If there be no increase in the sugar content the case is almost certainly not epidemic encephalitis. Of course it does not follow that if there is an increase the case is one of encephalitis, but it is one important point in favour of such a diagnosis.

Paralysis.—Paralysis or paresis of the facial nerve was noted in only a few cases in this outbreak. In my experience it was much more common in former epidemics. Paralysis of deglutition was also less commonly met with in the recent cases.

House Distribution.—In very few instances had we more than one case from one house. No member of the staff at either hospital contracted the disease.

Encephalitis during Pregnancy.—In the earlier outbreaks of encephalitis it was, I think, the general opinion that, if the disease occurred in a pregnant woman, the outlook was very grave. Very high mortality rates, even as high as 60 per cent., were recorded. In an early report of the Ministry of Health the death rate in such cases was given as 44 per cent. Larger experience has tended to modify this view, and evidence is gradually accumulating

that these high rates of mortality were exceptional; later records show a very much lower death rate. Among the 183 cases in our fever hospitals last spring there were ten cases in pregnant women, with one death—a mortality rate of 10 per cent.; this is lower than the case mortality in the whole series (11.4 per cent.). In only one of my cases was the pregnancy interrupted, although many were very severe. Two children born in hospital were healthy and have remained so.

PROGNOSIS.

In the earlier epidemics in Britain, the Continent, and America, in the years 1918 to 1921, the case mortality rates, calculated on the deaths in the acute stage, were everywhere high—up to 50 per cent. in some places. In the report of the Ministry of Health for 1919-20, which dealt with over 1,200 cases, the mortality was 48 per cent. Such figures are certainly misleading; they are arrived at by taking the number of cases notified and the total deaths certified. Everyone interested in the subject knows that, especially in the earlier years, large numbers of cases escaped notification. Professor Hall, in his very excellent work on *Epidemic Encephalitis*, published last year, says: "One may say that in every 100 cases 25 die, 25 recover practically completely, whilst 50 recover with residua"; adding that "Such a statement can only be taken as very crude." With larger experience the death rate in the acute stage is gradually being placed lower. In the 183 cases in the hospitals under my care in the spring of 1924 the case mortality was 11.4 per cent. It is very difficult to calculate the correct mortality rate—so many cases recover completely, or almost completely, for a time, some for a few weeks, some for months, and some for years, but sooner or later develop serious after-effects which prove fatal.

Percentage of Complete Recovery.—Very varying estimates have been given. After our first epidemic waves had passed I think the general opinion was that, roughly, 20 per cent. recovered completely. I have always been very sceptical about this recovery rate. As a result of further experience there has been a tendency to put this percentage lower and lower. My own belief is that the percentage of complete and permanent recovery is very small. In a recent discussion on encephalitis in one of the large cities in England the physician who opened it placed the complete recovery rate at 50 per cent.; but some of the subsequent speakers questioned this. I think such a complete recovery rate must be very exceptional. My own belief is that if we were to put the percentage of complete recovery at 5 we should at least be much nearer the mark. I am not forgetting that some patients which I had in hospital five or six years ago are still earning their living at their usual occupations and are reported well, but close inquiry has nearly always shown that all is not absolutely well with these patients; and I think that even now, after a lapse of five years, it is too soon to sound the "all clear" signal. Riddoch has reported the results in 83 cases which recovered from the acute attack in the London Hospital; they were examined at long intervals after discharge; he found "residua in almost all" (Hall). My own experience coincides with this.

Cause of the Lethargy.—The question of the cause of the lethargy cannot be answered at present. Several very ingenious hypotheses have been suggested. I shall briefly refer to a few.

I. That the lethargy is due to a "cut out" of the afferent stimuli to the thalamus. There is much to be said for this theory, and it is supported by many authorities whose opinion must carry weight.

II. That it is due to changes in the pituitary. Inflammatory changes in the pituitary—congestion, venous thrombosis, and necrosis—have been noted frequently *post mortem*. You will remember that Professor Symmers pointed out the frequent finding of such changes in the autopsies on the earliest cases seen here, several years ago. It has been held that under normal conditions the secretion of the pituitary counteracts fatigue. If this is correct

then any inflammatory process which decreases the secretion must increase fatigue and lead to drowsiness; and if there is permanent necrotic destruction this theory would explain the permanent loss of energy which is met with so often as an after-effect in these cases.

III. That there exists a definite "sleep centre," and that this centre becomes involved in the pathological process. Various authorities put forward this theory, and very different are the sites they suggest for this "sleep centre." Other authorities maintain that the lethargy of epidemic encephalitis has no relation to normal sleep.

IV. That it is due to blocking of the aqueduct, leading to dilatation of the ventricles with fluid and increased pressure.

Whatever may be found to be the true explanation I think it will certainly not prove to be due to blocking of the free passage of cerebro-spinal fluid through the aqueduct. My reasons for saying so are:

(1) If a lumbar puncture be made in a case showing deep lethargy and all the fluid which will flow drained off, it will be found that the amount is quite as large as will be obtained from puncture in a case of similar duration which does not show lethargy.

(2) If in a deeply lethargic case the puncture be repeated daily the amounts of fluid obtained will be approximately the same, 40 to 60 c.cm. being the usual amount.

(3) If in a deeply lethargic case a lumbar puncture be made and the fluid allowed to flow until only a few drops a minute come away, and if then the patient's head be raised from the pillow and the chin elevated, so as to allow further drainage of the ventricles, the flow through the cannula will immediately increase and a considerable additional amount of fluid will pass off.

(4) If in a deeply lethargic infant, with open fontanelles, a lumbar puncture be made, the flow of the fluid can be immediately and markedly increased by pressure on the fontanelle. Removal of the pressure instantly retards the flow, which increases again with renewed pressure on the fontanelle.

I have not yet met with a case in which these tests gave any different result, even when the lethargy amounted to complete coma of several weeks' duration. That being so I think that blocking of the aqueduct as the cause of the lethargy may be definitely ruled out.

TREATMENT.

The course is so irregular, and is subject to such wide fluctuations, such sudden improvement in symptoms, only to be followed by relapses, that it is exceedingly difficult to form anything approaching a correct opinion on the results obtained by any line of treatment. This being so, it is only natural to find in the medical journals from time to time very glowing and enthusiastic accounts of the results obtained by some new (or often very old) therapeutic measure.

Many of the treatments suggested, and even enthusiastically recommended, can only be described as weird in the extreme. Yet I fancy most of us who have been called upon to treat any considerable number of cases have, doubtfully, employed some of these extraordinary treatments, the rationale of which we could not see, only quickly to abandon them.

[Dr. Robb then reported his results with very many lines of treatment. He was not satisfied he obtained any good results with hexamine; sodium salicylate; "fixation abscess"; diphtheria antitoxin; intravenous injections of the patient's own cerebro-spinal fluid; frequently repeated lumbar puncture and drainage; intramuscular injections of sterilized milk; and intravenous injections of "argotrope" (1 per cent. colloidal silver and 20 per cent. hexamine), as suggested by Marburg and favourably reported upon by Professor Wimmer. Marked relief in chronic cases of Parkinsonism and disturbance of sleep followed the continued administration of 1/100 grain of hyoscine hydrobromide three times a day by the mouth, but it was not curative, and the symptoms quickly returned on suspension of the treatment.]

Concluding, Dr. Robb said:

As a result of my experience in attempting to treat these cases I find myself in complete accord with Professor Hall when he says:

"At present any reliable therapeutics, either for the disease itself or for its many after-results, does not exist."

At the same time it is true that a great deal can be done to relieve the very many present troubles these patients suffer from by the judicious use of palliative measures.

ENCYSTED PLEURAL EFFUSION CONTAINING CHOLESTERIN.

BY

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THE following case may be of interest on account of the unusual occurrence of a large amount of cholesterol in an encysted pleural effusion.

Corporal N., aged 34 years, came under our care at the British Station Hospital, Rawalpindi, towards the end of March, 1924. He was complaining of pain in the left side of the chest due to fibrinous pleurisy on that side. There were no symptoms pointing to any lesion on the right side of the chest. Examination, however, showed an area of dullness extending to about two inches above the liver dullness in the right axilla. This dull area fell short of the spinal column by about two and a half inches posteriorly. The breath sounds were diminished. The heart was not displaced. The temperature was normal, and there was no expectoration.

Paracentesis followed by aspiration was performed, and 25 ounces of a brownish shimmering fluid were withdrawn. It contained crystals of cholesterol. No organisms were found nor hooklets of *Taenia echinococcus*. A culture was sterile. A differential blood count gave the following result:

Polymorphonuclear leucocytes	...	...	69 per cent.
Lymphocytes	...	...	24 "
Large mononuclears	...	...	4 "
Eosinophils	...	...	2 "
Basophils	...	...	1 "

The urine showed no abnormality. Nothing could be found to account for the presence of the large amount of cholesterol in the pleural effusion. There was no history of any lung or liver trouble, or of dysentery.

The patient was later transferred to a hospital in a hill station for further treatment, and was discharged from there as a convalescent to light duty. He again came under our observation early in January, 1925. He was then feeling fairly well, but complained of breathlessness on exertion, and inability to do any heavy work. The heart's apex was well inside the nipple line in the fifth left intercostal space; the sounds were rather faint. The blood pressure was: systolic 136, diastolic 76 mm. Hg. The thorax did not move freely on respiration. No abnormality was noted in the left lung, but there was moderate dullness in the right axilla as high as the third rib; posteriorly it reached to within two inches of the spinal column. The breath sounds over the dull area were faint; there were no accompaniments; vocal resonance was diminished and slightly egophonic.

Paracentesis and aspiration were again performed, and 30 ounces of fluid very similar in appearance to that obtained on the previous occasion were withdrawn.

Pathological Report.—Smear negative to the tubercle bacillus. Culture sterile. Fluid contains a large quantity of cholesterol crystals. Some dullness remained after aspiration, and this showed a tendency towards increase. A fortnight later a second aspiration was performed, and a further 7 ounces of fluid were withdrawn.

Throughout the patient's stay in hospital the temperature was normal. There was no wasting, and no glandular enlargement. There was no increase in the respiration rate while the patient was at rest. The pulse varied from 68 to 100. The urine showed no abnormality.

X-ray examination on April 3rd, 1924, showed that at the base of the right chest there was a very dense shadow with a well marked, sharply defined upper margin, suggestive of an encysted empyema. The root shadows were heavy, with some slight increase of linear markings in both lung fields. There was no displacement of the heart, which was central and dystrophic. There was some impairment of excursion of the right diaphragm. After aspiration of fluid the upper margin of shadow was still well defined, but collapsed to the side of the chest.

General Observations on the Case.

1. No cause was discoverable to account for the presence of the cholesterol in the pleural fluid.
2. The effusion showed a marked tendency towards recurrence.
3. The effusion was encysted, and there was no apparent connexion with the liver.
4. In spite of very considerable effusion there was no displacement of the heart.