RESIDUAL VACCINES:

A NEW TECHNIQUE FOR THEIR PREPARATION, WITH A
DESCRIPTION OF SOME PROPERTIES OF THE
BACTERIAL RESIDUE.*

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THE detoxication of vaccines has recently attracted considerable attention. Thomson's method¹ depends upon the fact that alkaline solutions dissolve organisms and their toxins whilst mineral acids precipitate the organisms but retain the toxins in solution. The chief merit of this method is that the final concentration ready for administration can be adjusted to any desired strength. Professor H. R. Dean² has shown that a suspension of virulent organisms can be detoxicated by the action of eusol or hydrogen peroxide in weak solution. The author has found it convenient to employ a method which embodies these two principles.

The term "detoxicated" is unfortunately somewhat misleading, and has even caused this type of vaccine to be looked upon with a certain amount of suspicion in some quarters. It has been thought that a preparation which is itself non-toxic cannot be expected to stimulate a protective reaction on the part of the tissues. If this were so, these vaccines might with reason be suspected. But it can be shown that they possess a toxicity of a definite type, and that this toxicity is contained in the bacterial residue which remains after the complete removal of the toxins and endotoxins. It therefore appears to the author to be more in accordance with a true description of them to call them vaccines of the bacterial residue, or more briefly, residual vaccines. The term "toxin" as used to-day has a restricted meaning, and in order to avoid confusion the toxic properties of the residue will be, as far as possible, referred to as the residual toxicity rather than the residual toxin.

Technique.

A sufficient quantity of growth is usually obtained from two or three Petri dishes. The growth is emulsified with about 100 c.cm. of a 1 per cent. solution of phenol in sterilized tap water and the emulsion poured into a tall glass. The volume is noted and the number of organisms per cubic centimetre estimated. From a pipette sufficient 40 per cent. NaOH is added to form a 0.5 per cent. solution. The suspension is then set aside for an hour. During this time the suspension loses most of its opacity and becomes translucent, but rarely quite transparent. Strong HCl is next added drop by drop until the fluid is neutral to litmus, after which one drop of the acid is added for every 10 c.cm. of fluid, which is now opaque once more. Lastly, hydrogen peroxide (10 vols.) is added in the proportion of 1 c.cm. to every 50 c.cm. of suspension.

The vessel is placed in a 55° C. oven and remains there for twenty-four hours, at the end of which time the organisms are found lying at the bottom of the glass as a dull white precipitate. The supernatant fluid containing the oxidized toxins is clear, and should be decanted, leaving the deposit behind. More 1 per cent. phenol is now added to make the fluid up to its original volume and acid added as before—namely, 1 drop to every 10 c.cm. Peroxide is not added. Sedimentation is usually complete in three to six hours. The supernatant fluid is again poured away, the deposit neutralized by 40 per cent. NaOH, and the suspension made up to the required strength by the addition of normal saline, no further phenol being added, so that the final concentration contains phenol in a strength of 0.5 per cent. or less. Since tap water and not saline was present in the residue it might be thought that the final preparation is hypotonic, but the neutralization of the NaOH produces a solution of sodium chloride near enough to the strength of normal saline.

The strength per cubic centimetre and the dosage will depend upon the ratio of residual toxicity to the total toxins present in a culture grown upon a suitable medium. This ratio varies for different organisms, but a safe rule is to make the vaccine 100 times the strength of the corresponding ordinary vaccine, and to commence treatment with a small trial dose. No absolute rule can be laid down. The idiosyncrasy of the patient is just as evident with these vaccines, but as a rough guide it may be said that the initial dose of a residual vaccine should never exceed 1,500 millions.

* The expenses of the laboratory side of this work were assisted by a grant from the Department of Pathology, University of Manchester.

The last stage in the preparation is the sterilization, which is performed in the autoclave by heating for fifteen minutes at a temperature of 120° C. When the bottle is removed from the autoclave a fine precipitate is usually present, the supernatant fluid being almost clear. Both fluid and precipitate react normally to acids and alkalis; the deposit is easily passed into suspension again by slight shaking. Sedimentation is used instead of centrifugalization, because experience proved that to yield results a centrifuge must be of fairly large capacity and be capable of very high speed.

Sedimentation is slower, but the use of Dean's method reduces the washings to two and so tends to equalize matters. The oxidation method cannot be used alone because of its liability to produce a vaccine of inconveniently large bulk. The rate of sedimentation varies with different organisms, but the most refractory can be made to deposit quickly by boiling the alkaline solution for a minute or two, then adding the acid and setting aside in the 55° C. oven as usual. There is no need to repeat the boiling in subsequent washings.

How long the vaccine keeps without deterioration is uncertain, but it is much longer than is the case with thermolabile vaccines. The reaction of one particular vaccine was as strong as ever fifteen months after it was made; another, when nine months old, also showed no change in its toxicity.

Examination of the Precipitate.

The gonococcus was used to investigate solubility in NaOH. An emulsion containing approximately 1,000 millions per cubic centimetre was made with normal saline and a film examined. The cocci were of normal appearance. The suspension was converted into a 1 per cent. solution of NaOH. Much of the opacity immediately disappeared and the fluid became translucent, almost transparent. A film showed cocci present in large numbers with no amorphous deposit.

The suspension was next heated to 55° C. for forty-eight hours and resulted in a perfectly transparent fluid. A film showed cocci in greatly diminished numbers and a large amount of debris. It is difficult to give a precise estimate, but it seemed that about two-thirds of the cocci had disintegrated. It would therefore appear that the translucency is due to swelling of the organisms with an alteration in their light transmitting properties. True solution occurs later after comparatively prolonged action of the alkali. The observations were repeated with *B. coli* and gave similar results.

Reaction on Patients.

It is stated that the toxic symptoms seen with ordinary vaccines do not occur with residual vaccines. This is not in accordance with the author's experience. A local reaction is the most noteworthy feature. Shortly after inoculation a red area, slightly swollen, appears round the site of injection. It is commonly about three inches in diameter and painful to pressure, but not otherwise painful. The constitutional disturbance is variable, but in general is less than that seen with ordinary vaccines.

Clinical Results.

Over two hundred cases have been treated up to the present time, and according to reports received from the clinicians the results have been very satisfactory. There have been failures, but the results on the whole have been better than those one would have expected if the cases had been treated with the older type of vaccine. This is a facile statement, and one is aware that a detailed account is preferable. Circumstances arose by which more exact information was obtained.

A stock ordinary vaccine was required for a few men suffering from chronic bronchitis, and it was decided to treat a further number of patients with residual vaccine. These latter comprised that large group of cases of chronic bronchitis to be found attending the out-patient department of any large general hospital. They could not be said to offer much prospect of success with any form of treatment available to people in their station in life. Cases with severe cardiac or renal complications were excluded, otherwise no restriction was placed upon the age of the patient or upon the origin or duration of the disease; in fact for a period of six or eight weeks the out-patient department was drained for cases.

A large stock of a mixed suspension was collected, and from it was prepared an ordinary vaccine having the following composition:

M. catarrhalis (7)	...	...	70 millions per c.cm.
Streptococcus (4)	...	...	15 " "
Pneumococcus (4)	...	...	25 " "
Friedländer's bacillus (5)	...	...	50 " "
B. influenzae (3)	...	...	10 " "
Hoffmann's bacillus (3)	...	...	30 " "
M. pharyngis siccus (1)	...	...	10 " "
Staphylococcus (6)	...	...	20 " "

The figures in brackets denote the number of sources from which the organisms were obtained. For the sake of brevity this vaccine will be referred to as the "O" vaccine.

The remainder of the stock was converted into a residual vaccine by the method previously described, except that it was divided into three parts, which were each sterilized in a different way. The first part was sterilized at 55° C. by means of 1 per cent. phenol acting at that temperature for twenty-four hours. This was called the "X" vaccine. The second portion was sterilized by heating at 95° C. for sixty minutes, and was called the "S" vaccine. The third part was sterilized in the autoclave, and called the "A" vaccine. Except for the method of sterilization these three vaccines were identical, and were made 100 times the strength of "O."

At this point it might be objected that any merit this type of vaccine may possess is due to a small amount of toxin which has escaped removal. In the case of "X" it would be 1/100th part of that originally present in "O" if, as was the case, the reaction caused by a given volume of either was approximately the same. The point can be discussed forthwith.

When a suspension is detoxicated by simple solution and sedimentation, the deposit is usually in volume 1/10th to 1/15th of the supernatant fluid, and the soluble toxins present in the water of the deposit will therefore be 1/10th to 1/15th of the total toxins originally present. But if the washing is repeated six times, the amount of toxin remaining will be considerably less than one millionth part of their former amount, if simple mechanical washing is the whole explanation.

Further, the reaction is not appreciably less if the organisms are washed twelve times instead of six, or if the author's combined method is used. Lastly, the suggestion does not explain the oxidation process in which the peroxide is evenly distributed throughout the suspension. The theory will not meet the facts. Most bacterial toxins are destroyed by a temperature of 80° to 90° C. The behaviour of the residue will be seen later.

A Series of Chronic Bronchitis Cases.

The results are presented in tabular form, and the intensity of the reactions and the amount of clinical improvement are shown by numerals which have the following significance:

Local Reactions.

0=No reaction.

1=Swelling, no pain; possibly tender on pressure.

2=Swelling with erythema; painful, and stiff on movement.

3=As in 2, but more pronounced. Erythema more than 3 in. in diameter. Shooting pain along arm in addition to pain at site of injection.

General Reaction.

0=No reaction.

1=Slight lassitude, but no definite malaise.

2=Patient feels unwell, with headache and disinclination for food. Malaise disappears in twenty-four hours.

3=Malaise more marked and lasting two or three days.

Degree of Improvement.

0=No improvement.

1=Slight, but clinically evident improvement.

2=Moderate improvement with paroxysms of coughing much diminished.

3=Marked improvement with complete, or almost complete, cessation of nocturnal asthmatic attacks.

Note.—The improvement was estimated by the physician to whom the case belonged and who was not informed as to what type of vaccine the patient had received, or the dosage.

"O" Vaccine.

Patient.	Age.	Duration of Disease in Years.	First Dose.			Last Dose.			Number of Doses Given.	Degree of Improvement.
			Amount in Minims.	General Reaction.	Local Reaction.	Amount in Minims.	General Reaction.	Local Reaction.		
L. 4	40	3	2	1	1	14	2	0	6	0
S. 16	51	7	1	0	0	18	2	0	7	1
A. 4	38	5	2	1	0	17	2	1	3	3
A. 2	46	4	2	2	1	16	3	3	3	3
A. 3	40	4	2	2	1	16	3	3	6	1
L. 6	47	4	2	2	1	18	2	0	7	2
L. 14	50	5	2	1	0	18	1	0	6	1
L. 7	35	2	2	1	0	17	2	1	6	1
S. 18	38	3	2	3	2	10	3	0	6	3
Average improvement 1.66										

"X" Vaccine.

Patient.	Age.	Duration of Disease in Years.	First Dose.			Last Dose.			Number of Doses Given.	Degree of Improvement.
			Amount in Minims.	General Reaction.	Local Reaction.	Amount in Minims.	General Reaction.	Local Reaction.		
L. 1	35	4	4	1	2	15	2	3	7	3
L. 2	42	4	4	1	2	17	1	1	7	3
L. 3	46	4	4	1	2	17	1	1	7	3
S. 2	32	4	4	1	2	10	1	1	7	3
S. 3	38	4	4	1	2	13	1	1	7	3
S. 4	44	4	4	1	2	11	1	1	7	3
S. 5	36	4	4	1	2	11	1	1	7	3
S. 6	48	4	4	1	2	11	1	1	7	3
S. 7	43	4	4	1	2	11	1	1	7	3
S. 8	35	4	4	1	2	12	1	1	4	4
S. 9	41	4	4	1	2	13	1	1	4	4
S. 10	21	4	4	1	2	11	1	1	4	4
S. 11	23	4	4	1	2	11	1	1	5	5
S. 12	23	4	4	1	2	11	1	1	5	5
S. 13	23	4	4	1	2	11	1	1	5	5
S. 14	23	4	4	1	2	11	1	1	5	5
S. 15	23	4	4	1	2	11	1	1	5	5
S. 16	23	4	4	1	2	11	1	1	5	5
S. 17	23	4	4	1	2	11	1	1	5	5
S. 18	23	4	4	1	2	11	1	1	5	5
H. 5	37	1	1	0	0	10	0	0	6	6
H. 6	38	1	1	0	0	10	0	0	6	6
H. 7	35	1	1	0	0	10	0	0	6	6
H. 8	42	1	1	0	0	10	0	0	6	6
Average improvement 2.21										

"S" Vaccine.

Patient.	Age.	Duration of Disease in Years.	First Dose.			Last Dose.			Number of Doses Given.	Degree of Improvement.
			Amount in Minims.	General Reaction.	Local Reaction.	Amount in Minims.	General Reaction.	Local Reaction.		
S. 8	39	5	2	0	1	13	1	2	7	3
L. 22	41	5	2	2	2	7	1	2	5	3
H. 6	38	4	2	0	1	9	1	1	4	4
A. 1	35	4	2	1	2	7	2	2	4	4
L. 9	39	3	2	1	2	10	1	1	5	5
L. 15	46	6	2	1	2	9	1	1	5	5
Average improvement 2.16										

"A" Vaccine.

Patient.	Age.	Duration of Disease in Years.	First Dose.			Last Dose.			Number of Doses Given.	Degree of Improvement.
			Amount in Minims.	General Reaction.	Local Reaction.	Amount in Minims.	General Reaction.	Local Reaction.		
S. 9	36	4	4	1	2	14	2	3	7	3
S. 11	41	4	4	1	2	15	1	1	5	5
S. 12	43	4	4	1	2	11	1	1	5	5
L. 10	47	4	4	1	2	11	1	1	5	5
L. 11	43	4	4	1	2	14	1	1	5	5
L. 12	33	4	4	1	2	11	1	1	5	5
L. 17	28	4	4	1	2	11	1	1	5	5
L. 18	39	4	4	1	2	11	1	1	5	5
L. 19	42	4	4	1	2	11	1	1	5	5
L. 20	44	4	4	1	2	11	1	1	5	5
L. 21	35	4	4	1	2	11	1	1	5	5
S. 14	43	4	4	1	2	11	1	1	5	5
A. 5	34	4	4	1	2	11	1	1	5	5
L. 23	41	4	4	1	2	11	1	1	5	5
L. 8	36	4	4	1	2	11	1	1	5	5
L. 16	36	4	4	1	2	11	1	1	5	5
S. 17	37	4	4	1	2	11	1	1	5	5
L. 24	44	4	4	1	2	11	1	1	5	5
L. 13	33	4	4	1	2	11	1	1	5	5
L. 25	47	4	4	1	2	11	1	1	5	5
H. 9	36	4	4	1	2	11	1	1	5	5
H. 11	34	4	4	1	2	11	1	1	5	5
H. 12	34	4	4	1	2	11	1	1	5	5
H. 4	36	4	4	1	2	11	1	1	5	5
H. 3	36	4	4	1	2	11	1	1	5	5
H. 10	38	4	4	1	2	11	1	1	5	5
Average improvement 2.30										

It is recognized that this method of presenting the facts is open to criticism, but it is the only way in which the records of such a large number of cases can be kept within reasonable limits. The use of the minim scale was determined by the available supply of hypodermic syringes.

Analysis of Results.

The "O" results are not put forward here to demonstrate that residual vaccines are superior to thermolabile vaccines—as in fact they are—but to afford a comparison of the general and local reactions, and hence of the toxicity.

The average of the general reactions in the "O" group is slightly greater than that in the "X," "S" and "A" groups, but the local reactions in these latter exceed those in the former group, and are possibly to be explained by the imperfect solution of the bacterial debris with consequent slow absorption, this in turn necessitating a strong local reaction to break it up and pass it into solution.

The reactions of the "A" group prove that a temperature of 120° C. is not detrimental to a residual vaccine, so the "S" results are superfluous, and should be read as part of the "A" group.

A very noticeable feature of the constitutional disturbance caused by the residual vaccines was the frequency with which it was of an intestinal nature. Whenever a "G.R. 3" was produced a disinclination for food was invariable, and in about half the cases was accompanied by some vomiting and diarrhoea. The latter symptoms disappeared in eight to twelve hours after their onset. Diarrhoea alone and of mild degree was common also with milder reactions, but only after the first or second dose. The gastro-intestinal disturbance was never seen in the "O" group, and it would therefore appear that bacterial residues differ from thermolabile toxins in their physiological action as well as in their chemical properties. This phenomenon has been observed with other vaccines of the same type, but only when either the pneumococcus or streptococcus was contained in the vaccine.

Another point which is brought out in the tables is the size of the last dose given. It will be noticed that the "O" group reached an appreciably higher number of minims than any other group, and during the course of treatment one could not help observing that the "O" group tolerated much greater percentage increases of dosage. When weighing this fact it should be recollected that all four groups started with the same number of minims to which they reacted to approximately the same extent.

It is a common method when using thermolabile vaccines to increase each dose by 30 to 40 per cent. above the preceding dose, and one therefore works by a geometrical progression; the method is not applicable to residual vaccines, or is so only within narrow limits. The patient cannot tolerate such increases.

The dose should be increased by some fixed amount—which was two minims in this particular series—and even then many patients required the same dose repeated once in order to establish a comfortable tolerance. It was abundantly clear that the defensive mechanism of the tissues found a greater difficulty in dealing with the toxicity of the residue.

The improvement after each dose of all the residual vaccines was greatest after the first three or four. The later doses produced a much slower improvement until it ceased altogether after the seventh dose or thereabouts. It is hoped to investigate this further at a future date. The extent of the benefit, as well as the reactions, in the "X," "S," and "A" groups is equal, and is a further proof that heat is not detrimental to the residue. The simplicity of sterilization in the autoclave compared to the usual gentle heating and subsequent testing by cultural methods is obvious.

Nature of the Toxic Substance in the Residue.

It will be apparent that the residue contains a toxic substance. Vaughan³ has shown that certain toxic bodies, apparently allied to proteins, can be obtained from bacteria, and that these bodies withstand a much higher temperature than do toxins and endotoxins. It has further been shown that some degree of immunity can be created against them, and that the local reaction when they are injected is intense. The precise origin of the toxicity may be somewhat vague, but it is evident that the residue possesses some properties which show fundamental differences from those of thermolabile toxins, and which are striking enough to justify one in separating the residual toxicity from the endotoxins.

The two cardinal features which distinguish the class are:

1. They are not rendered inert by weak solutions of oxidizing agents.
2. Their toxicity is neither destroyed nor impaired by a temperature of 120° C.

In this investigation the extent of constitutional disturbance has been taken as the standard by which to compare the toxicity of the residue with that of the thermolabile toxins. It is a reasonable physiological test, but it should be remembered that it is only a measure of the relative toxicity; it affords no indication of the relative weights of the two classes present in a culture or of the relative toxicity of the types if equal weights of each are taken.

The dose of an ordinary vaccine depends upon the amount of toxin present. The strength is stated in organisms per cubic centimetre because that is the only method of measurement available, unreliable as it is. The number of organisms is no real guide to the dose, for different strains of the same organism vary enormously in toxicity, and the amount of toxin produced by any given strain varies with the medium upon which it is grown. It is not possible to standardize the thermolabile toxin, for that substance is very unstable and becomes inert from many causes, all of a comparatively trivial nature. If the toxin is standardized when the vaccine is made, the result may be worthless in less than a month. Furthermore, the production of toxin is not an essential metabolic process, so the destruction of it does not necessarily incommode the organism at all. Antitoxins will neutralize toxins and nothing else.

It is true that a thermolabile vaccine contains bacterial protein, but only because of its accidental and unavoidable presence as part of the organism which accompanies the toxin. Its amount is small and the actual quantity quite indefinite. In effect the patient is immunized against the toxins. The destruction of the organism is left to the tissues to manage as best they can.

The rationale underlying residual vaccines rests upon a more solid basis. In these the toxic substance against which immunity is produced is the tissue protein of the organism itself, the preservation of which is essential to the life of the parasite, and the vaccine is therefore designed to strike at the primary cause of the disease; if the causal organism is destroyed its toxin can be ignored, for it will disappear whether the patient destroys it or does not.

The counting of the organisms in a residual vaccine yields information which remains accurate, the relationship of the toxic residue to the organisms being a fixed ratio, and since the residue is very stable, its toxicity does not change with age.

Finally, the therapeutic results obtained with these vaccines are more uniform. The degree of improvement is quite as great in the most promising cases, and a larger proportion of the cases benefit by the treatment. Almost all the cases in this series were drawing either a pension or sick pay, and this fact undoubtedly influenced their own estimation of the benefit received. Physical signs may be negligible or altogether absent, but it is impossible to disprove that a man still has a cough, and for this reason no case has been entered as cured. It is fairly certain that the estimates of the improvement are not unduly sanguine. This aspect of the work was realized from the start, but previous experience with the vaccine had inspired a belief that it would justify itself even under a handicap that amounted to an unfair test.

Since it has been shown that the effect of heat upon the residue is nil, the "X," "S," and "A" sections can be amalgamated into one large group in which the clinical benefit derived from residual vaccines can be demonstrated in a short table:

	Degree of Improvement.			
	Nil.	Slight.	Moderate.	Considerable.
Total number of cases treated, 52	3	9	13	27
Percentage	6	17	25	52

CLINICAL NOTES.

Chronic bronchitis as a distinct entity is especially prevalent in Manchester and Salford. Many cases date from an attack of acute bronchitis contracted on active service in France. Attacks of a spasmodic or asthmatic type are very frequent. The expectoration varies greatly in different cases, but is usually abundant and mucopurulent.

The physical signs include marked diminution of expansion and respiratory capacity, hyper-resonant percussion note, and widespread mixed râles and rhonchi. There is marked deterioration in health and capacity for employment, and as a rule there is evidence of cardiac muscle weakness.

In the presence of such changes in the physical state of the chest, and probably of permanent changes in the anatomical structure of the lungs, the influence of vaccine treatment must necessarily be limited, but several salient facts emerge from observation of a series of cases treated in this manner:

1. In most cases there is distinct improvement in the patient's general condition, in colour, vigour, and capacity for activity.

2. The sputum, which may at first increase in amount, in practically every case diminishes in quantity and loses its mucopurulent character, becoming white and less profuse.

3. The cough becomes less persistent and the attacks or paroxysms much fewer and less severe, particularly those occurring in the night and early morning.

4. A striking feature has been relief from asthmatic attacks; from the clinical point of view this is the most conspicuous effect produced by the treatment.

The clinical observers have not known the type of vaccine employed in any given case, and the results must speak for themselves.

Summary.

1. It is not possible, short of gross destruction, to detoxicate completely a suspension of pathogenic bacteria.

2. The residual toxic substance is not affected by a temperature of 120° C., it is not destroyed by weak solutions of oxidizing agents, but it is precipitated by mineral acids.

3. It is possible to remove from a suspension of organisms all the thermolabile toxins and endotoxins. Thomson's method, Dean's method, or that of the author are equally efficient.

4. It is probable that the residual toxic body is an integral part of the bacterial protoplasm.

5. Residual vaccines can be sterilized in the autoclave, so sterilization is simple and certain.

6. Residual vaccines are highly efficient therapeutic agents.

7. They retain their maximum efficiency indefinitely.

8. Most cases of uncomplicated chronic bronchitis respond to treatment by residual vaccines.

The author cannot conclude without acknowledging his indebtedness to Professor Dean for much valuable advice and constructive criticism, and to the physicians who contributed the clinical notes for their kindness in undertaking the large amount of clinical work which this investigation required.

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ENCEPHALITIS LETHARGICA.

BY

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[AFTER a brief reference to the history of the disease, and the use of the term "encephalitis lethargica," Dr. Haynes quoted a classification of the symptoms given by Dr. F. M. R. Walshe in *Brain*, November, 1920. The primary division was into general symptoms and nervous symptoms. General symptoms were such signs of toxic infection as fever, eruptions, malaise, pain, headache, and gastrointestinal disturbance. The nervous symptoms were general or focal, and in each case were classified as

positive or negative, the terms being employed in the sense in which Hughlings Jackson originally used them.]

Positive symptoms are expressions of exalted function, either from irritation or loss of higher control, and negative symptoms express depression or loss of function. The general positive symptoms in lethargic encephalitis are delirium, restlessness, hallucinations, and so on; the general negative symptoms lethargy and coma. The focal positive symptoms are convulsions, involuntary movements and muscular contractions, ataxy, rigidity, and pain; the focal negative symptoms are paralyses.

Recognition of these two classes of symptoms—positive and negative—is very helpful, enabling us to understand that a lesion of a single area might give rise to convulsions as well as to paralysis, and that whether a clonic twitching of a muscle or weakness occurred depended not on the site, but upon the nature of the lesion.

The disease occurs at all ages, and affects both sexes equally. Three stages can be distinguished—the prodromal stage, the acute stage, and the stage of regression. The incubation period has not yet been determined. The chief prodromal symptoms, which last usually from one to seven days, but may be prolonged for three weeks, are headache, giddiness, lethargy, blurred or misty vision, and diplopia; vomiting is not common; muscular weakness frequently occurs.

The acute stage is characterized by fever (101° to 102° F.), lasting from two to five days or longer, the pulse and respiration being as a rule unaffected. The patient lies in bed semi-conscious and immobile, or with much muscular asthenia; the face is expressionless and mask-like; the limbs in many cases are rigid, and in some they remain in any position in which they are placed, as in the condition known as *flexibilitas cerea*. Usually patients can be roused from their stupor to take food or to answer questions; this they do intelligently, but in a voice often nasal and monotonous, the sentences being uttered very slowly. There may be emotional irritability, and nocturnal delirium frequently occurs. In this stage muscular twitchings and tremors may occur. There is no characteristic skin eruption, though petechiae, papules, or erythema have been observed; one case was notified as scarlet fever and another as measles. *Tache cérébrale* is readily elicited in most cases. Other symptoms are dysphagia, nausea, and constipation; the tongue is dry and coated. Retention or incontinence of urine is of frequent occurrence; the urine is concentrated, loaded with urates, and transient albuminuria is found during the febrile stage.

Paralysis of the cranial nerves is a characteristic feature the third and seventh being most commonly affected. The fundus oculi is normal. Ptosis is the usual form of third-nerve paralysis; it may be unilateral or bilateral, and slight or complete. The ciliary muscle is often involved early and paralysed longer than other ocular muscles; the pupils may be unequal; divergent or convergent squint is seen; diplopia is common. Whereas ptosis and strabismus are only transient, involvement of the movements of the eyeball may last several weeks, as may disturbance of accommodation. Facial paralysis has often been observed; it is, as a rule, bilateral, but more marked on one side than the other; the tongue and pharynx are sometimes affected and deafness has been noted.

Netter's statistics place the frequency of lethargy and ocular palsies as high as 75 per cent. of all cases, but, though with fever this is the characteristic syndrome, a large number of cases do not conform to this type; some begin with excitement and muscular twitchings or spasms, or with severe pains in the limbs; others have quiet delirium with delusions; others, again, go about with persistent headache, apathy, and lack of facial expression. In fact, as Farquhar Buzzard has pointed out, an inflammation of the encephalon can produce as many symptoms as there are functions of the brain.

Of the lethargy, which is an interesting feature of the disease, three explanations have been suggested: (1) That it is due to internal hydrocephalus, the result of occlusion or partial occlusion of the aqueduct of Sylvius by inflammatory processes in the region of the corpora quadrigemina. It is noted that sluggishness or total abolition of the pupillary reflexes frequently occurs with the lethargy, and that this combination is characteristic of tumours of the posterior end of the third ventricle. (2) That it is due to interference with the afferent paths of stimuli from the

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