

her skin and mucous membranes were pale. Amenorrhoea lasted for five months during the summer of 1920. No treatment beyond rest was adopted at this time.

In March, 1921, she felt sufficiently well to begin nursing again, but became ill again after three weeks' work. There was nothing of any importance in the family history. She had an attack of colitis nine years previously. Most of her teeth had been extracted, but she had a good artificial set with a few sound teeth of her own. No glossitis was present. She was very weak and pale; she had no other abnormal signs or symptoms, but the temperature was 100.2°.

On April 12th the result of a blood count was: Erythrocytes 1,232,000; leucocytes 1,750; haemoglobin 20 per cent.; polymorphs 53 per cent., eosinophils 1 per cent., lymphocytes 45 per cent.; colour index 0.85.

Marked poikilocytosis and anisocytosis were present, with a preponderance of microcytes. Moderate polychromatophilia and some basic stippling were observed. Two nucleated reds, both megaloblasts, were seen while counting two leucocyte films.

She was given novarsenobillon, 0.2 gram, intravenously, and the oral administration of beta naphthol, 5 grains twice daily, was commenced. Up to April 13th she had regular normal actions of the bowels, but after that date they were never open again except by enemata. The temperature rose, with morning remissions, until it was 104.4° on April 14th, falling by lysis until it reached 96.6° on April 21st. On April 14th cultures were sown from a catheter specimen of urine and a specimen of faeces. The former showed the *Staphylococcus albus* only, the latter *B. coli* only. On April 15th the patient became delirious and lay in a semi-conscious condition. On April 19th novarsenobillon, 0.1 gram, was given by intramuscular injection. On April 22nd her temperature was still subnormal, so half a pint of citrated blood from healthy and compatible donors was given intravenously. She recovered consciousness for about an hour, but her temperature again rose, and she died on April 25th, 1921.

The autopsy showed the following pathological changes. "Tabby-cat striation" was present on the columnae carnae of the heart. The liver showed fatty change, and excess of iron was present. The kidneys showed fatty degeneration, their surfaces were finely granular, and the capsules adherent.

The appendix was empty, with an apparently congenital occlusion of the lumen at its proximal end. About five feet above the ileo-caecal valve there was a sharp line of demarcation in the interior of the small intestine, but no constriction was present. Above this line the appearance was that of normal jejunum, below it normal ileum. The appearance at this place was as if an end-to-end anastomosis had been performed, but the patient had never undergone an abdominal operation. The line itself appeared to consist of a fine ring of small ulcers. Microscopic sections showed a simple ulceration of the mucous layer, the other layers being normal.

A section of the spleen showed slight fibrous change, with atrophy of the Malpighian tufts. Films of bone marrow showed some hyperplasia of the erythroblastic elements.

CASE II.

The second case was that of C. D., aged 58, a coachman. He came under our care on January 15th, 1921, with a history of diarrhoea and vomiting during the past seven weeks, accompanied by slight jaundice during the earlier part of that period. His past history was that he had two attacks of influenza about fifteen years previously, a severe attack of diarrhoea four years previously, followed by occasional milder attacks.

His appearance was cachectic and his mucous membranes were very pale. His teeth were dirty, but seemed sound otherwise. Emphysema of the lungs almost obliterated the cardiac dullness. Some scabbing was present in the right nostril, and a small polypus was found at the anterior end of the middle turbinal bone. This gave rise to a clear mucous discharge which was sterile. A blood count was taken on January 17th, with the following result: Erythrocytes 1,240,000; leucocytes 4,400; haemoglobin 35 per cent.; polymorphs 20 per cent., eosinophils 0, lymphocytes 80 per cent.; colour index 1.4. Marked poikilocytosis, extreme anisocytosis, and an abundance of macrocytes were observed. Seventeen nucleated reds, including five megaloblasts, were seen. Most of the reds showed nuclear remains. The patient was given haemoglobin and malt, 1 drachm thrice daily, also beta naphthol 5 grains twice daily. He started weekly intravenous doses of novarsenobillon 0.2 gram. The following pathological tests were made: Wassermann, negative; faecal examination, excess of fatty crystals; faecal culture, coliform bacilli and Gram-positive diplococci; urinary culture, a few sarcinae.

A blood count on February 3rd showed some improvement: Erythrocytes 1,528,000; haemoglobin 46 per cent. On February 16th the count was worse than the original one. This was attributed to a somewhat severe reaction after each dose of novarsenobillon. The dose was reduced to 0.1 gram, which produced no untoward symptoms, and has been gradually increased to 0.2 gram, which is being given at the present time. By April 8th he was again improving: erythrocytes 1,776,000. On April 4th an x-ray examination showed that the fangs of the lower lateral incisors were rather bulbous. These were extracted under a general anaesthetic with special antiseptic precautions, and yielded a pure growth of streptococci. A course of autogenous vaccine was given until June 13th, followed by a course of stock streptococcal vaccine. On June 28th the count was as follows: Erythrocytes 3,216,000; leucocytes 5,600; haemoglobin 65 per cent.; polymorphs 22 per cent.,

eosinophils 2 per cent., lymphocytes 76 per cent.; colour index 1.0. Fairly marked poikilocytosis and polychromatophilia. Six normoblasts, no megaloblasts.

The patient now enjoys good health, having the novarsenobillon and vaccine weekly. Time alone will show whether this is genuine recovery or a remission.

The points which we wish to emphasize about these two cases are the history of colitis in the first case and of diarrhoea in the second. In the first case a definite ring of ulcers was found in the intestine, and in the second an infective focus in the teeth. Novarsenobillon seems to be a valuable drug in this disease; the value of the autogenous vaccine cannot be estimated as it was given concurrently with other treatment. Evidence of alimentary derangement was also present in a fatal case of pernicious anaemia following dysentery which we treated in 1920. There was a history of alimentary derangement in a case of aplastic anaemia and a case of pernicious anaemia which Dr. Rivaz Hunt has kindly allowed us to quote. The latter appears to be enjoying normal health under treatment with novarsenobillon.

EIGHTY-NINTH ANNUAL MEETING

OF THE

British Medical Association.

Held at Newcastle-on-Tyne, July, 1921.

SECTION OF PHYSIOLOGY, PHARMACOLOGY, THERAPEUTICS, AND DIETETICS.

H. H. DALE, C.B.E., M.D., F.R.S., President.

BEFORE proceeding to the business of the Section, Dr. H. H. DALE and Professor A. V. HILL gave two eloquent appreciations of the work and character, both as a physiologist and as a man, of the late Professor J. A. Menzies, Vice-President of the Section, who died only a few days before the opening of the Annual Meeting of the Association. It was decided that a resolution expressing the "deep sense of the loss medical science has sustained by the death of Professor James Acworth Menzies, Professor of Physiology in this University, and Vice-President of this Section," should be conveyed to the University, and that in addition a message of respectful sympathy should be sent to Professor Menzies's widow.

THE USE OF THE HOT WIRE FOR INVESTIGATING THE TIME RELATIONS OF THE PULSE AND THE CHARACTERISTICS OF VOLUNTARY CONTRACTION IN MAN.

BY

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[Abstract of Communication.]

A VERY fine platinum wire (of diameter about one-hundredth of a millimetre) is mounted in a tube which is connected to a tambour or funnel placed upon the subject's artery. The wire is heated to just below redness by an electric current. The rise of temperature in the wire raises its electrical resistance, which, however, is lowered each time a pulse of air comes along the tube and cools the wire. The pulses of air caused by the movements of the artery, therefore, cause corresponding changes in the resistance of the wire, and a continuous record of the latter is therefore also a continuous record of the movements of the artery. The electrical resistance of the wire may be recorded in one of three ways:

1. By a Wheatstone's bridge arrangement and a string galvanometer. The hot wire is placed in the fourth arm of the bridge and the other resistances are so adjusted that no current passes through the string galvanometer, and therefore the string is not deflected. When the resistance of the hot wire changes, the balance is upset and

a current passes through the string, the deflection of which is recorded upon a moving photographic plate.

2. By having the hot wire in the primary circuit and the string galvanometer in the secondary of an electrical transformer. When the resistance of the hot wire changes there is an alteration in the intensity of current passing through the primary, and this causes an induced current through the galvanometer, which is recorded in the same way.

3. By a similar condenser arrangement.

The principal advantages of the instrument are that there is extraordinarily little time lag between events taking place at the artery and the corresponding movement of the string; that the time relations of the pulse can be very accurately measured, and that the records are not contaminated by artificial effects due to independent mechanical vibrations of the recording instrument itself. Vibrations of this kind can be detected in tracings, obtained by the usual mechanical methods, by comparing them with records obtained in this way. The velocity of the pulse wave can be measured very accurately by means of two hot-wire sphygmographs, one of which is placed on the carotid pulse, the other on the radial. If generally required for this purpose it would be possible to replace the costly string galvanometer by a much cheaper arrangement.

The same apparatus can be modified so as to record the movements of human muscles when contracted voluntarily. A convenient way to show the effect is to hold a tambour between the first and second fingers and to press on its surface with the thumb. Whether the tambour is pressed gently or vigorously the photographic records show oscillations varying from 40 to 50 per second. Different subjects give different frequencies of oscillation, but the same subject gives a frequency which is constant and independent of the particular instrument used. From these and other control experiments it is argued that the oscillations observed do not owe their origin to independent vibrations of the instrument itself. When the tongue is pressed against the tambour, oscillations of the same characteristic frequency are again observed. This eliminates the possibility that they may be caused by mechanical creaking at joints. The frequency of oscillation corresponds closely with the frequency of the electric change in voluntary contracting muscle observed by Piper.

The nature of these records, and of the Piper electro-myograms, suggests tentatively an interesting property of the cells which constitute a centre in the nervous system. These must discharge their impulses at the same frequency and in the same phase as one another; otherwise the muscular contraction and the electrical variation would both inevitably be continuous instead of periodic. Moreover, according to the all-or-none law, when a muscle enters into moderate contraction a certain number of its fibres contract fully, whilst the remainder continues entirely passive. The absence of fatigue in a moderately contracting muscle suggests that if a moderate contraction is prolonged, the first group of active fibres is relieved by a second group which up till then have been passive. After a further interval the second group is in its turn relieved, and so on. Records obtained during health suggest that the transition from one group of fibres to another occurs quite smoothly, but that in old age, fatigue, and possibly in functional diseases of the nervous system, it cannot be accomplished so accurately, and tremors appear.

DISCUSSION.

Dr. MARTIN suggested that the application of the hot-wire sphygmograph to the investigation of cases of aneurysm would prove very fruitful.

Dr. G. A. CLARK suggested that it might be possible by this method to follow the passage of the contraction wave down the auricle.

Dr. H. H. DALE reminded Dr. Clark that Lewis had already succeeded in doing this by attaching a set of hairs to the auricle. It would be well to reinvestigate by this method Sherrington's work on the relative strength of the muscular contraction induced (a) by direct stimulation, and (b) by reflex stimulation. He pointed out to Dr. Martin that many hospitals possessed an electrocardio-

graphic instalment which could be easily modified to this purpose, and, further, that the method would be a very convenient one for the bedside.

Professor A. V. HILL pointed out, in reply to Dr. Martin, that variations of temperature in the rubber tube connecting the tambour to the hot wire had no appreciable effect upon the records, and that of the three methods described in the paper he had found the Wheatstone bridge most satisfactory. In reply to Dr. Dale, he considered that adventitious sounds in the room where observations were being made would not affect the records at all.

THE ETIOLOGY AND TREATMENT OF VARICOSE ULCERS.

BY

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AND

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THE causation of varicose ulcers is generally regarded as due to a local depression of tissue resistance in the region of the affected veins, dependent on a local nutritional deficiency. The treatment is usually purely local, consisting of such mechanical means as bandaging, or of the external application of stimulant lotions or ointments, in order to promote tissue growth and repair. In the series of cases under consideration a new aspect of the pathology of this condition is put forward, and also a means of procuring satisfactory results by treatment in a relatively short time. With one exception all the cases were varicose conditions, either ulcers or eczema; the remaining case was that of an old wound of the leg which had broken down and ulcerated.

In a previous paper, published in the *Journal of Physiology*,¹ it has been shown that the calcium of normal unclotted blood is present in two forms; of a total of 10.7 mg. p.c., roughly 4 mg. are present in a combined or non-ionized form, and 6.7 mg. are present in the ionic state. After clotting has taken place, the total ionized calcium was found to be 10.7 mg. p.c., so that normally all the calcium of the serum should be ionized. In all the present cases it was found that there was a deficiency in the ionized calcium, though the total calcium was not very markedly reduced. The inference to be drawn, therefore, is that some of the calcium which should be ionized has become combined with some unknown substance, formed at some stage of the pathological process in question. It suggests, further, that the ulceration may be due to this deficiency of the ionized calcium, and treatment was therefore directed towards supplying the deficiency.

The first form of treatment used was the intramuscular injection of calcium chloride dissolved in distilled water, 1 grain being injected once a week, or in some cases at shorter intervals. Details of this method of treatment will be found in a paper on the use of calcium salts in haemorrhage.² The results obtained were not satisfactory, and only one complete cure was obtained in these ulcer cases. A tolerance to the calcium injections appeared to become established, so that progress was only obtained by increasing the amount and frequency of the dose. Improvement or retrogression of the ulcer ran roughly parallel with the rise or fall of the ionized calcium content of the blood. To summarize, this form of treatment was beneficial up to a certain point, but required considerable time and patience, and even then its results were by no means certain.

The second form of treatment used was the combination of calcium injections with the oral administration of thyroid gland substance. This produced effects which were not markedly different from those obtained with the injections alone. It cannot be said that the thyroid had of itself any beneficial effect. In one or two cases calcium salts given by the mouth were substituted for the injections, but the effect was not only entirely negative in respect of improvement, but even harmful.

Parathyroid gland substance (Parke, Davis), gr. 1/10 by the mouth daily, was next used, and with this treatment an

immediate improvement seemed to take place. The ionized calcium of the serum rose rapidly to the normal figure, and the local condition showed early signs of healing; it was found unnecessary to continue the calcium injections. In cases treated with parathyroid alone seven to fourteen days seemed to be the period required for the drug to produce its maximal effect, though the time taken for complete healing to occur was of course dependent on the size of the ulcer. In putting this treatment into practice, gr. 1/10 of the parathyroid substance is given daily until healing has occurred, and then twice a week for three or four weeks. In this series of cases, and also in other cases, no signs of overdosage became evident, even though the patient was taking parathyroid for several weeks without intermission. When firm healing has occurred the patients are told to report at once any irritation round the site of the ulcer, and if the ionic calcium is again decreased a further short course of parathyroid may be prescribed.

The local treatment of the ulcers was of the simplest type, in order not to prejudice the action of the internal treatment. The ulcers were covered with plain gauze or boracic lotion, though in some cases no dressing at all was used. It must be remembered that the calcium deficiency is but one factor in the condition, and that for the maintenance of efficient tissue nutrition, and therefore healing, the circulation and drainage of the part must be assisted. It was for this reason found that the best results were obtained when the patient was kept in bed; if cases are allowed to go about their usual business healing is very much retarded, and as the parathyroid also relieves the pain and irritation of the affected part, the ulcers are neglected and may become grossly infected. Again, the best results are obtained with early cases of ulceration or varicose eczema rather than with long-standing ulcers, where local fibrosis has interfered with the blood supply to the ulcerated area. It was found that early cases treated with parathyroid and confined to bed healed up with quite remarkable rapidity.

The fact that parathyroid administration has so great an effect in causing these ulcers to heal seems to point to the possibility that a partial deficiency of the parathyroid secretion may play some part in their causation, and this supposition is strengthened by the fact that the parathyroids are recognized regulators of calcium metabolism. The true reason for this failure of parathyroid activity must be a matter of conjecture. It is possible that two factors play a part: first, that varicose ulcers commonly occur in middle-aged patients, especially females, at a time when degenerative changes are most apt to become evident; and, secondly, that the continued stagnation of the blood in a chronically varicose area may produce in time a general poisoning, as such blood must be overloaded with the products of tissue breakdown.

It may not, therefore, be unreasonable to suggest that varicose ulceration is another instance of the vicious circle in disease. The toxic agents produced by the varicose condition may be supposed to affect the parathyroid glands, and are also able to combine with some of the calcium of the blood which is normally ionized. The calcium balance of the blood is thus disturbed, and the damaged parathyroids are unable to readjust it. This deficiency of ionic calcium may cause a lowering of vitality of the tissues, so that chronic ulceration or eczema occurs at the point where nutrition is worst. Ulceration leads to a further absorption of toxic material, and so the circle is completed. The aim of treatment is to break it; calcium alone seems unable to do so, probably because it is only able to affect the particular symptom of calcium deficiency, and does not act upon the primary cause—an erring metabolism. Parathyroid, on the other hand, has apparently a more fundamental action: not only can it act specifically upon the calcium metabolism, but it may also produce an improvement in the general metabolism through the medium of the endocrine system as a whole.

It is not yet possible to state that all chronic non-malignant ulcerative processes are of the same type. It has, however, been found in the small number of cases examined that chronic gastric ulcer conforms to the same type of calcium deficiency. Further, such cases are undoubtedly improved by the administration of parathyroid substance, so that there are indications that two chronic

ulcerative conditions, differing widely in locality and in the symptoms they produce, may yet have a common biochemical relationship.

Case 1.—Female, aged 45; varicose ulcer. Before treatment the ionized calcium content was 6.19 mg. p.c.; on the seventh day of treatment by injection of CaCl_2 gr. 1 it was 6.93 mg. p.c.; on the thirteenth day 7.23 mg. p.c.; and on the twenty-seventh day 10.58 mg. p.c. On the forty-first day the ulcer was completely healed. Four months later it was still healed; some irritation of ankle. Ionic calcium = 8.66 mg. p.c.

Case 2.—Female, aged 55; extensive ulcer encircling leg completely. The progress of the case is shown in the following table:

| Day of Treatment. | Treatment. | Ca mg. p.c. Serum. | | | Progress. |
|-------------------|--|--------------------|--------|--------|--------------------------|
| | | Com- bined. | Ionic. | Total. | |
| 0 | Before treatment | — | 4.83 | — | Improved. Healing. |
| 7 | CaCl_2 inject. gr. 1 | — | 6.06 | — | |
| 15 | " " | — | 5.38 | — | |
| 21 | " " | — | 8.07 | — | |
| 29 | " " | — | 6.06 | — | Enlarging. Spreading. |
| 36 | Injections stopped | — | 7.74 | — | |
| 43 | " " | — | 8.47 | — | |
| 50 | " " | — | 7.74 | — | |
| 57 | " " | — | 6.90 | — | |
| 81 | CaCl_2 gr. x per os t.d.s. | — | 5.22 | — | |
| 88 | Inject. recommenced | — | 5.70 | — | |
| 92 | " " | — | 6.33 | — | |
| 104 | " " | — | 6.61 | — | |
| 113 | CaCl_2 per os stopped | — | 6.01 | — | |
| 123 | CaCl_2 gr. 2 inject. (on 118th day) | — | 6.93 | — | |
| 127 | " " | 2.08 | 6.93 | 9.01 | Eczema. |
| 133 | " " | 3.01 | 6.01 | 9.02 | |
| 138 | " " | 2.05 | 6.62 | 8.67 | |
| 145 | " " | 1.65 | 6.01 | 7.66 | |
| 153 | " " | 2.39 | 6.62 | 9.01 | |
| 166 | CaCl_2 gr. 2; and thyroid gr. 2½ | 2.47 | 6.62 | 9.09 | |
| 172 | " " | 3.24 | 5.77 | 9.01 | |
| 179 | " " | 3.26 | 5.77 | 9.03 | |
| 185 | " " | 2.48 | 7.32 | 9.80 | Eczema gone. |
| 194 | " " | 2.08 | 7.70 | 9.78 | |
| 201 | CaCl_2 and parathyroid gr. 1/10 | 0.94 | 8.66 | 9.60 | |
| 208 | Parathyroid only | — | 10.1 | 10.1 | |
| 215 | " " | — | 10.4 | 10.4 | |
| 223 | " " | — | 10.4 | 10.4 | |

Completely healed on the 237th day.

Case 3.—Female, aged 42. Treatment and progress:

| Day of Treatment. | Treatment. | Ca mg. p.c. Serum. | | | Progress. |
|-------------------|--|--------------------|--------|--------|-------------|
| | | Com- bined. | Ionic. | Total. | |
| 0 | Before treatment | 3.44 | 6.61 | 9.45 | Healing. |
| 4 | CaCl_2 inject. gr. 1 | 3.03 | 6.01 | 9.01 | |
| 10 | CaCl_2 inject. gr. 2 | 1.69 | 7.35 | 9.03 | |
| 15 | " " | 1.29 | 6.98 | 8.27 | |
| 22 | " " | 0.48 | 9.45 | 9.93 | Stationary. |
| 30 | " " | 0.48 | 9.45 | 9.93 | |
| 43 | " " | — | 9.92 | 10.10 | |
| 49 | CaCl_2 and thyroid gr. 2½ | 1.00 | 8.66 | 9.66 | |
| 56 | " " | 1.78 | 7.70 | 9.48 | Healing. |
| 63 | " " | 1.36 | 8.44 | 9.80 | |
| 71 | " " | 1.39 | 7.61 | 9.00 | |
| 78 | CaCl_2 and parathyroid gr. 1/10 | 2.06 | 7.70 | 9.76 | |
| 85 | Parathyroid only | — | 10.1 | 10.1 | Healed. |
| 100 | " " | — | 10.4 | 10.4 | |

Case 4.—Male, aged 58. Treatment and progress:

| Day of Treatment. | Treatment. | Ca mg. p.c. serum. | | | Progress. |
|-------------------|--|--------------------|--------|--------|---------------------------------------|
| | | Com- bined. | Ionic. | Total. | |
| 0 | Before treatment | 3.50 | 5.51 | 9.01 | Slow improve- ment. |
| 7 | CaCl_2 inject. gr. 1 and thyroid gr. 2½ | 3.08 | 6.01 | 9.09 | |
| 10 | Ditto | 2.28 | 6.35 | 8.63 | |
| 21 | Ditto | 3.18 | 6.30 | 9.48 | |
| 28 | Ditto | 1.54 | 8.26 | 9.80 | Stationary Rapid im- provement. |
| 35 | Ditto | 1.65 | 7.35 | 9.00 | |
| 41 | Parathyroid only, gr. 1/10 | 1.14 | 8.26 | 9.40 | |
| 49 | " " | — | 10.1 | 10.1 | |
| 56 | " " | — | 10.4 | 10.4 | Rapid im- provement. |
| 64 | " " | — | 10.4 | 10.4 | |

Case 5.—Male, aged 30; old wound of leg, broken down and ulcerated. Treatment and progress:

| Day of Treatment. | Treatment. | Ca mg. p.c. Serum. | | | Progress. |
|-------------------|--|--------------------|--------|--------|-------------|
| | | Combined. | Ionic. | Total. | |
| 0 | Before treatment | 2.89 | 5.75 | 8.64 | |
| 13 | CaCl ₂ inject. gr.1 and thyroid gr.2½ | 2.13 | 7.35 | 9.48 | |
| 18 | Ditto | 2.66 | 6.35 | 9.01 | Improving. |
| 25 | Ditto | 2.73 | 6.30 | 9.03 | |
| 32 | Ditto | 1.54 | 8.23 | 9.80 | Stationary. |
| 40 | Ditto | 1.59 | 8.26 | 9.78 | |
| 46 | Parathyroid only, gr. 1/10, from 43rd day | 1.14 | 8.66 | 9.80 | |
| 54 | | 1.01 | 8.98 | 9.99 | Improving. |
| 61 | | — | 10.4 | 10.4 | |
| 69 | | — | 10.4 | 10.4 | Healed. |

Case 6.—Female, aged 30; varicose eczema. Before treatment the total calcium content was 10.77 mg. p.c. serum (combined, 2.69; ionic, 8.08). On the eighth day of treatment by parathyroid only, gr. 1/10, the combined calcium was 1.90; ionic, 8.00; total, 9.90 mg. p.c. serum. The irritation was lost after a week's treatment.

Case 7.—Male, aged 74; varicose ulcer of four years' standing. Before treatment the total calcium content was 9.70 mg. p.c. serum (combined 3.10; ionic, 6.61). On the eighth day of treatment by parathyroid only, gr. 1/10, the total calcium was 9.17 mg. p.c. serum (combined, 1.09; ionic, 8.08); on the fifteenth day the total was 9.32 mg. p.c. (combined, 0.66; ionic, 8.66). The ulcer was healing well, and the patient was up and at work.

Case 8.—Female, aged 64; three ulcers, each the size of a five-shilling piece; erysipelas and a thrombosed vein. Before treatment the total calcium content was 9.98 mg. p.c. serum (combined, 2.71; ionic, 7.27). On the fifteenth day of treatment by parathyroid only, gr. 1/10, the ionic calcium was 10.1 mg. p.c. serum. The patient was completely healed in ten days.

REFERENCES.

¹ Vines, *Journ. of Physiol.*, 1921 (55), 85. ² Grove and Vines, *BRITISH MEDICAL JOURNAL*, 1921.

DISCUSSION.

Dr. DALE asked whether any reasons were known why the calcium ion concentration of the blood was so closely related to ulceration. In reply Dr. GROVE said that he knew of none, but regretted the absence of Mr. Vines, who had been more connected than himself with the theoretical aspects of the work. Dr. DALE also asked whether any investigations of the effect of ulceration on the clotting time of the blood had been made. Dr. GROVE replied that none had been made. Dr. Dale further drew attention to the difficulty of obtaining parathyroids from sheep and oxen. This was confirmed by Dr. MARTIN.

Dr. CLARK asked whether similar changes in the calcium ion concentration of the blood took place in septic conditions. On this, again, no work had been done.

ANAPHYLATOXIN.

BY

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(Abstract.)

It is generally agreed that anaphylaxis is due to the formation of an antibody which combines with reinjected antigen. One theory attributes the symptoms caused by the reinjection to the occurrence of this combination in the cells. According to this view antibody in the blood is protective. The other theory supposes that union of antigen and antibody in the blood causes the formation there of a toxic substance, anaphylatoxin. Many methods of imparting such toxicity to guinea-pig's serum have been found, most of them having little direct relation to anaphylaxis. Dale and Kellaway have examined the nature of the change taking place in serum when it is rendered toxic by incubation with starch agar, etc. They find no evidence of protein cleavage, nor any change of viscosity or surface tension corresponding to the appearance of the toxicity. "Anaphylatoxin" does not act directly on plain muscle, as it should in theory, but it acts by producing changes in the blood of the nature of the changes which precede clotting. An animal can be

rendered immune to "anaphylatoxin" by a subfatal dose, and its serum will transmit this immunity to another guinea-pig; but this guinea-pig, if previously anaphylactic to an antigen, retains its sensitiveness unimpaired.

Excess of antibody added to the saline bath in which anaphylactic plain muscle is suspended will protect it from the antigen. The author regards the similarity of the symptoms produced by "anaphylatoxin" to those of the true anaphylactic reaction as superficial and misleading, and adheres to the theory which attributes anaphylaxis to antibody located in the cells.

OBSERVATIONS ON CERTAIN ELECTRICAL SIGNS OF THE HUMAN BODY.

(Preliminary Note.)

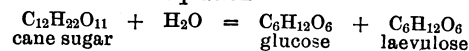
BY

M. C. POTTER, M.A., Sc.D.,

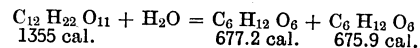
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ON a former occasion¹ it has been shown that an E.M.F. amounting to 0.5 volt is developed when cane sugar is fermented through the action of yeast. As is well known, this reaction takes place in two stages: first the inversion of the cane sugar by means of invertase, and secondly the conversion of the glucose and laevulose into alcohol and CO₂. In both these reactions an E.M.F. is developed. In the inversion of the cane sugar the E.M.F. was 0.03 volt. It may be objected that the E.M.F. developed in the second stage is due to the bubbling of the CO₂ through the fermenting liquid. But no such objection can be raised in the case of the inversion of the cane sugar. Hence it follows that the E.M.F. developed during fermentation cannot entirely be due to bubbling.

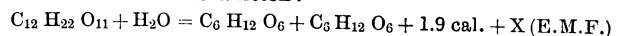
If we consider the equation



from the point of view of energy, we find that the heat of combustion of the cane sugar is 1355 cal., while that of the glucose is 677.2 cal., and of the laevulose is 675.9 cal. The equation becomes



and it is seen that 1.9 cal. are liberated during the inversion of the cane sugar. The equation, however, is incomplete without a consideration of the electrical energy, and therefore should be written:



where X is a constant at present undetermined. There is thus a liberation of both thermal and electrical energy.

It will be noticed that the action of the invertase is from a state of higher to one of lower potential—that is, it acts as a catalyst through the conversion of potential into kinetic energy. At present synthetic enzymes are unknown, and it would seem improbable that they exist, for if an enzyme were to act synthetically a supply of energy would be required for its operation.

Again, it is known that in the formation of a carbohydrate, during photosynthesis from CO₂ and H₂O, thermal energy is locked up and becomes latent, to be again liberated when the carbohydrate is broken down, as for instance, in respiration or muscular exercise. From the fact that E.M.F. is also liberated during the breaking down of carbohydrate, it must now be recognized that electric energy also becomes latent in the carbohydrate, and it follows that there are endo-electric and exo-electric reactions analogous to the endo-thermic and exo-thermic reactions.

Should this explanation prove correct it follows that all the variations of E.M.F. in the plant or animal are due to synthetic or catalytic reactions. The energy utilized in muscular contraction being principally derived from carbohydrate, it would seem that the E.M.F. developed during muscular contraction is proportional to the amount of carbohydrate utilized and further proportional to the work done.

It has been stated previously that the arterial and venous bloods possess a contrary electrical sign.¹ Unfortunately, in the experiments upon which this conclusion was based the air or carbonic acid was not passed through a strong electric field, so that further investigations are necessary before a definite conclusion can be reached on

this point. But, just as the CO_2 produced in alcoholic fermentations is ionized,² it is only natural to expect that the CO_2 liberated during muscular contraction is also ionized and that the ions are to be looked for in the venous blood. As there are both synthetic and catalytic reactions taking place in the human body, some experiments have been initiated to determine the E.M.F. of the human body and of the breath. In the method adopted the person under observation stands upon a platform, insulated by means of ebonite feet, and is connected with either a Laby-Burton string electrometer or a Wilson portable electroscop.

The Body.

The E.M.F. of the body has been found to be subject to great fluctuations in the same person, and further variations in E.M.F. exist between different individuals. Thus in a class of 29 students 10 exhibited a negative and 19 a positive reaction. In the same individual the E.M.F. has been found to vary from 10 volts negative to 3 volts positive with certain neutral points. At present it has not been found possible to construct a curve showing these variations.

The Breath.

The breath has been found to be negative in normal cases.

(a) When standing on the insulated platform and blowing through a glass tube, the drops of condensed breath were allowed to fall upon a wire connected to the electrometer. The electrometer then responded in the negative direction. An objection, however, can be raised to this method, as the capacity of the instrument would be changed.

(b) Upon a sheet of paper soaked in melted paraffin two similar pieces of tinfoil were pressed, opposite to each other, one on each side. One tinfoil plate was then breathed upon. The electrometer responded as these tinfoil plates were made to approach or recede from the electrometer. The one breathed upon indicated a negative and the other a positive reaction.

(c) A small glass tube, the edge coated with paraffin, the inside and outside coated with tinfoil, rested in the hollow of a block of paraffin. The inside tinfoil was connected to the electrometer. When breath was allowed to condense upon the outside, by blowing through a glass tube, the electrometer then moved in the positive direction.

The same effects can be observed when platinum is substituted for tinfoil. Experiments (b) and (c) show that small Leyden jars can be charged with the human breath. The E.M.F. of the breath measured in this manner is approximately 1 to 2 volts negative.

(d) A silk tassel, when electrified positively by being drawn through a sheet of rubber, is readily discharged by the breath; but when electrified negatively by rubbing with a glass rod it is not discharged by the breath.

Crowded Rooms.

Some attempts have been made to compare the electrical changes in crowded rooms. Thus an aerial of thin copper wire has been arranged in a lecture room and measurements taken of the electrical state of the air before, during, and after lecture to a crowded audience. As far as experiments have progressed it would appear that the air is electrified negatively by the expiration of those present in the room. May it be that electrons in the discharged breath are to be regarded as excreta?

REFERENCES.

¹Electrical Effects accompanying the Decomposition of Organic Compounds, *Proc. Roy. Soc., B*, vol. 84, 1911. ²Electrical Effects accompanying the Decomposition of Organic Compounds: II, Ionization of the Gases produced during Fermentation, *Proc. Roy. Soc., A*, vol. 91, 1915.

DISCUSSION.

Professor A. V. HILL suggested various control experiments to test the validity of Professor Potter's explanation of the electromotive forces he had observed in these enzyme reactions. For instance, in the case of the E.M.F. observed between yeast and glucose solution inside the porous pot and glucose solution outside, one ought also to inquire whether an E.M.F. was observed between yeast and a neutral solution (on which it does not react) inside and the same neutral solution outside. In regard to the observations upon the E.M.F. between the breath and the body, Professor Hill was sceptical as to

how far these were not artificial effects due to the electric forces which are always present in a large town. He quoted instances of how his own work had been seriously interfered with by factors of this kind. He suggested that the observations should be repeated far out in the country so as to avoid such disturbances.

Professor POTTER, in reply, expressed his gratitude for these criticisms and suggestions, some of which he had already carried out.

On Thursday afternoon Professor Potter gave a practical demonstration, in the Botanical Laboratory, of the experiments described in his paper. Several members of the Section attended the demonstration and were much interested in it.

THE POISON ORGANS AND VENOMS OF VENOMOUS FISH.

BY

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I BEG to acknowledge the honour you do me in allowing me to address you on a subject which has interested me many years. Unfortunately our English textbooks on medicine contain little reference to the subject, and what they do contain is mostly incorrect. And even in such valuable textbooks as the *Cambridge Natural History* (1904) we find that the knowledge is not more advanced than can be obtained by reading Botard's work, published in 1889. Since that date much work has been undertaken, and among the most important communications on the subject are articles by Porta, Kobert, and the chapters on Poissons Venimeux in Calmette's work on Venoms. Experiments on fish venoms have been undertaken by Briot and others, yet an authority like Professor Ray Lankester published in 1910 an article on poison wounds, and stated that the evil effects of wounds inflicted by the sting-ray were due to the poisonous slime of the skin of the fish, and also that there was no definite poison sac in the weever fish.

From early times the question of true venoms in fish has been a disputed subject. Aristotle mentions several dangerous fish, notably Trygon, the sting-ray, and Scorpaena, but he was not explicit as regards the venomous nature of the sting, and he made no mention of the weever as a stinging fish. We first find precise information about fish with poison organs in the vast compilation of Pliny. He says Araneus (probably *Trachinus araneus*), a kind of weever found in the Mediterranean, "carries on its back a sting which is very dangerous, but there is nothing more terrible than the sting that arms the tail of Trygon, called Pastinaca by the Latins, which is five inches long. When driven into the root of a tree it causes it to wither. It can pierce armour like an arrow, it is strong as iron, yet possesses venomous properties." When we come to the Renaissance we find Belon, Rondelet, Salviani, and Gesner possessing exact ideas concerning Trygon, Trachinus, and Scorpaena. Speaking of Trygon, Pierre Belon describes the dart at the root of its tail, which is sometimes double and triple, with which it pricks those who touch it carelessly.

Rondelet describes the dart at length. Its margin is armed with teeth like the teeth of a saw, which enables the dart to enter easily, but tears the flesh as it is withdrawn by the backward slant of the teeth. Superstition and romance surrounded this dart with mysterious attributes. As Sir Thomas Browne quaintly remarks, it is conceived of special venom and virtues. If burnt, and the cinders applied to the wound in vinegar, it acts as an antidote. It relieves toothache, and helps cases of difficult dentition. If attached to the navel of a woman it causes her to have an easy childbirth, provided it be taken from a living ray, which is then thrown back into the sea. Aldrovander endeavoured to shake off the yoke of antiquity, and adopted the attitude of even modern writers. "I have searched," he says, "for a poison organ and have not found it; therefore, it does not exist," and proceeds to state: "These fish are dangerous only on account of the mechanical wounds they make and the depths to which their spines penetrate." More modern ichthyologists—Sonnini, Lacepede, and Cuvier—deny the presence of poison glands

in fish. Lacepede on every possible occasion denies the existence in the sting-ray, weever, scorpaena, plutosus, and muraena of any poison organ, and just as energetically Cuvier supports him, but allows that the pricks of certain fish are dangerous and produce acute pain. The opinion of these authors became almost a matter of dogma, and the works of ichthyology since their time have always denied the presence of a poison organ in fish.

Towards the middle of the last century Alman (1841) first described the gland at the root of the spine of the lesser weever, and his discoveries were widened and confirmed by Byerley, Gunther, Newton Parker, Bottard, and Schmidt. But even Bottard will not allow the sting-ray to possess a poison organ, and the *Cambridge Natural History* states that among the Elasmobranchs the eagle-rays and sting-rays have barbed serrated spines on the tail which inflict wounds far more severe than those caused by mere mechanical irritation, but except the mucus secreted by the gland cells of the skin, which may possess venomous properties, no special poison-forming gland is at present known. Porta a few years since described a poison gland in the sting-ray, but his description and plate does not convince me that he has yet correctly observed this very fleeting organ. I will, however, first show you the poison gland of the spiny dogfish, which was first described by myself in February, 1920. I have reason to believe that a German investi-

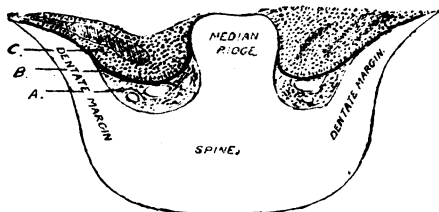


FIG. 1.—Section of spine of sting-ray (diagrammatic). Each groove is filled with A. alveolar connective tissue; B. pigment layer; C. epithelial layer, which consists of columnar and ovoid cells which secrete a venom which is discharged on to the tip of the teeth.

gator has written on that subject, but in spite of many efforts I have been unable to get on the track of his paper, which was referred to by Kobert as about to be published.

Fish inflict wounds by means of poison spines developed in connexion with their fins, usually the dorsal fin or with the gill cover or operculum. In certain Siluridae there is an axillary gland situated near the base of a pectoral spine, and in the plaice there is a spine situated ventrally which is reputed to be of a venomous nature. The spines at the root of the tail in sting-rays is in some cases developed apart from a fin, but there is reason to believe that in these cases it represents a fin, and, so to speak, takes its place. Bottard described three types of spines, but recent work brings the number up to six. Starting with the earliest type of fish, we have two kinds found among the Elasmobranchs.

Taking the spiny dogfish or spur-dog, we have a curved spine in relation to the anterior margin of its dorsal fin which is grooved on the posterior aspect extending a variable distance from the base. This groove contains a glandular structure, extracts of which can be proved to be venomous. The dart growing at the root of the tail in the sting and eagle rays is more or less flattened, and the lateral margins are serrated with teeth projecting towards the base. Facing the tail the spine has a central ridge, and a groove on either side exists between this ridge and the serrated margin. In these grooves lies a glandular structure.

In the bony fish the class Scorpaenidae contains several fish with poison glands, among which the weever is the best known type. Here we have the dorsal fin with spinous rays grooved anteriorly and posteriorly, and sheathed. At the bottom of this sheath is a definite poison gland. At the posterior margin of the gill cover is a more formidable spine deeply grooved above and below, and also surrounded by a sheath, which only exposes a small portion of the tip. At the base of the sheath lying partly in a bony, conical cavity, partly only surrounded by soft tissue, is a pear-shaped gland. In Synanceia the poison organ is still more developed. Each dorsal spine is

in its terminal half provided with a deep groove on either side, at the lower end of which lies a pear-shaped bag containing milky poison, the sac of which is prolonged into a membranous duct lying in the groove and open at its point. Finally, we have the perfected organ of *Thyllasophryne*, in which the operculum and two dorsal spines are the weapons. The former is narrow and styliform, and perforated from its base to its extremity, like the venomous fang of a snake. A sac at the base of the spine discharges its contents through the apertures and the canal in the interior of the spine.

The injection into roach of filtered glycerin extract of the gland substance obtained by scraping the groove of a dogfish's dorsal spine gave the following results: In most cases there was a period varying from ten to thirty minutes in which the fish lay quiescent, and during this period the respirations became very rapid, from 120 to 140 per minute. The general symptoms usually then subsided, but locally swelling and oedema occurred at the site of injection and the scales became erect over this area; no suppuration occurred. The fish, however, seemed ill, as it lost its pale colour and became dark and dull-looking, like fish allowed to remain too long in a live-bait can. In three fish I have observed definite symptoms of local paralysis of a spastic nature. The fish swam lying on the side of injection or else swam towards the inoculated side owing to the excursions of the tail taking place away from

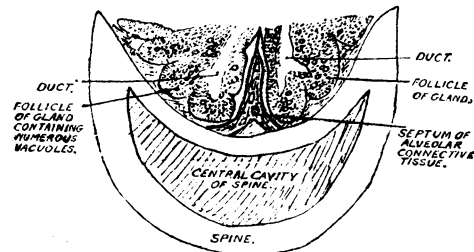


FIG. 2.—Section of spine of spur-dog or picked dogfish (diagrammatic).

the lesion. The fish were curved sharply towards the site of inoculation. In one fish I noted muscular spasms extending upwards from the tail and in another complete paralysis involving all the body to the level of the pectoral fins. Death appeared to be due to respiratory failure, and locally there was a pink oedema, but no haemorrhages, local or general.

Compare with these effects the action of weever venom on a goldfish as described in my paper in the *BRITISH MEDICAL JOURNAL*, 1906. It produces a local mortification of the tissues. When injected into the region of the lateral line, the fish is sharply bent away from the lesion on account of the predominant action of the lateral muscles of the opposite side. *Post-mortem* examination showed extravasated areas of blood at the site of inoculation, necrosis of muscle, and great congestion of the peritoneum. In mouse and guinea-pig inoculation under the skin of the back produced paralysis of the hind-quarters and similar local lesions. The haemolytic properties of this venom have been fully studied. It produces haemolysis without the addition of heated serum, but if it is mixed with glycerin and filtered through filter paper or through a porcelain candle, heated serum must be added to produce haemolysis.

In studying the paralytic effect of weever venom on white-blood corpuscles or the leucotoxic effect I have modified Wright's method of determination of opsonin. In making these experiments I took a volume of washed corpuscles, plus serum, plus a bacterial emulsion of *Staphylococcus aureus*, and a volume of salt solution in one capillary tube, and in the other the washed corpuscles, serum, bacterial emulsion and salt solution containing a drop of venom. After incubating for a quarter of an hour, the white cells in the poisoned tube, when stained in a film by Jenner's stain, showed vacuolation, deficient staining, and a marked diminution in the phagocytic action, 25 per cent. fewer bacteria being present in the count. As the bacteria stained equally well in each film, there was no reason to assume that this was due to bacteriolysis and not to a paralytic effect on the white cells. Considering how frequently secondary septic inflammations result from

the sting of these fish, these experiments would show how readily the barrier of phagocytosis may be broken down and the pathogenic organism from the dirty skin may find an entry into the system.

Treatment.

The question of treatment is of considerable importance, and the various empirical methods recommended are worthy of study. The fallacies of empiricism are not limited to the lay public, and a superficial reasoning is responsible for some of the methods in vogue even by the profession. For example, the injury is called weaver sting; the ant's sting is supposed to be due to formic acid—which is certainly open to doubt—therefore ammonia, being an alkali, will counteract the acid sting of both ant and weaver. It is the natural tendency for a person when injured to look round for something handy to apply. Among the natives of Mauritius and Reunion, where a similar stinging fish, the *Synancia*, frequently injures the feet of the fishermen, the natives fly to the leaves and seeds of plants growing by the seashore, in the same way as a person stung by a nettle flies to a dock leaf. Thus we find a local specific in the root and leaves of the datura, belonging to the family of Solanaceae used by these natives, not without effect, in soothing the pain, but probably in an entirely empirical fashion, as the datura grows in abundance on the dry sand of the shore.

Among the plants employed in an empirical way to cure the prick made by the fish the seeds of *Abrus precatorius* seems, according to Bottard, to have the virtue of a specific. We are familiar with abrus or jequirity seeds as a remedy for certain chronic eye diseases; a toxin, abrin, derived from it has been shown to possess the characters of the toxins of diphtheria and tetanus, to which are allied the toxins of snake and various other animal poisons. It dissolves red blood cells, and has also a neurotoxic effect. Why should one toxin be a cure for the symptoms produced by another toxin?

To investigate this point I made experiments on haemolysis with weaver venom, using various strengths of a solution of abrin in the mixture of washed corpuscles and venom. I found a definite diminution of haemolysis in those tubes containing abrin which appeared to be due to its powerful agglutinative action. Some experiments on small laboratory animals were not encouraging, as the toxic effect of abrin overshadowed any neutralizing effect on the poison.

To come to the local methods of treatment. We find that the fishermen have acted on the line of heat. The most frequent remedy is to plunge the part into boiling vinegar; another plan is to hold the affected limb over the funnel of the boiler which, in a smack, drives the donkey engine. A third plan is to apply heat vicariously by throwing the offending weaver on the fire, with what results I am unable to state. Sometimes they soak a piece of brown paper in vinegar, let it dry, and, wrapping the paper round the finger, apply a light and let the paper gradually smoulder until the heat becomes no longer bearable. The effect of heat, no doubt, would tend to destroy the venom. Another not infrequent treatment consists in cutting out the fish's liver and applying it to the wound. Here again we are approaching a scientific treatment by an empirical method. We have it recorded that serpent's bile appears to be an antidote to serpent's venom, and also that a preparation of snake's liver is of value in the treatment, not only of snake-bite, but also of some disease toxins, as of tetanus and diphtheria. It is probable the efficiency of the liver preparation is due to the cholesterol it contains. The BRITISH MEDICAL JOURNAL of 1906 records two cases of tetanus treated successfully with injections of cholesterol, and it has been established by Preston Kyes that cholesterol markedly inhibits haemolysis by cobra venoms and cobra venom lecithin. It also inhibits haemolysis by arachnolysin.

When we come to the best methods of destroying the active properties of venom we find that, as with snake venoms, potassium permanganate, chloride of lime, and chloride of gold destroy the venom rapidly, and I have suggested that all smacks and drifters should be provided with a Lauder Brunton snake-bite lancet (which at one end contains potassium permanganate crystals), so that a really efficient remedy may be at hand. Both practical and experimental treatment by this method have been shown to be accompanied with the best results.

The method I now employ with immediate success, both as regards relief of pain and toxic after-effects, is to inject several minims of a 5 per cent. solution of potassium permanganate (which I have kept in sterile ampoules, provided by Brady and Martin of Newcastle) into the punctured wound with a hypodermic syringe. In these days of rustless needles this method can also be recommended for fishermen; with such needles and the solution in ampoules there need be no more septic hands and amputated fingers, the result of injuries produced by fish venoms.

DISCUSSION.

Dr. H. H. DALE, in thanking Dr. Evans for his most interesting paper, congratulated him on the enthusiasm and energy which had enabled him to find time, amidst the arduous duties of general practice, to carry out these most important researches. He also complimented Dr. Evans on the beautiful series of microphotographs which had been shown by the lantern. In particular, he expressed much curiosity as to why a meshwork of pigment was found in the cells where the secretion of poison takes place.

Dr. HELE asked for reasons why immediate relief from the sting of the eagle ray was obtained by local injection of potassium permanganate and formol.

Dr. EVANS attributed it to the destruction of the toxalbumins (which are very labile) either by oxidation—in the case of potassium permanganate, or by reduction—in the case of formol.

PHYSIOLOGY OF ORAL HYGIENE.

BY

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To understand properly the physiology of oral hygiene it is necessary to refer briefly to the physiology of mastication, for, although the chief function of mastication is the preliminary preparation of food in order to facilitate its digestion, it has a secondary function in that when suitable foods are masticated it cleans the teeth and facilitates the action of the saliva in doing likewise. It should be noted, however, that many foodstuffs which are consumed at the present day are hardly subjected to the process of mastication at all. The food is simply taken into the mouth, receives a general squash between the teeth, or between the dorsum of the tongue and the hard palate, and is then swallowed. This method of mastication, if mastication it can be called, is as a rule adopted for custards, fine meal porridge, soft puddings, and soft non-fibrous foods generally.

When there is a certain amount of crisp, spongy, or fibrous matter in the foodstuff, then the process is essentially different, and mastication is performed in a more thorough manner. In this latter case the food is crushed and torn between, and heaped on to the masticating surfaces of the teeth by the muscular contractions of the tongue, cheeks, and lips, and by the motions of the lower jaw. During comminution between the teeth, the juices of the foodstuffs, the saliva which becomes incorporated, and the suspended non-fibrous part, are pressed out from the fibres and gradually collect during the process on the middle of the dorsum of the tongue, which is gradually hollowed out for the reception of such food, and this part is then swallowed. The fibrous part of the food, however, is subjected again and again to the crushing and disintegration between the teeth. The rubbing of the food on the teeth, the motions of the tongue, lips, cheeks, and mandible materially aid in the mechanical cleansing of the teeth and gums provided suitable food for this purpose is eaten. When for any reason mastication is not performed on one side of the mouth, the teeth on that side become coated with mucus, tartar, and food debris. It is evident, therefore, that mastication of fibrous food is conducive to dental hygiene.

Now let me direct attention more particularly to mucus and saliva in regard to oral hygiene. I shall do so at some length because the subject is not referred to in physiological textbooks. Physiologists hardly seem even

yet to realize that oral hygiene is a physiological process, and that all the glands opening into the mouth, together with their secretions, are specially adapted for the maintenance of oral hygiene, and that these secretions are scarcely, if at all, of importance for any other function.

Mucus.

From the point of view of the oral hygienist, the supposed function of the mucus for lubricating the bolus of food so as to facilitate its passage down the oesophagus is whimsical, for inasmuch as the function of mastication is to comminute the food, and reduce anything in the nature of a bolus to a liquid or semi-liquid state before it passes to the back of the dorsum of the tongue, there is no bolus to lubricate. The mucus and saliva are thoroughly incorporated with the food, and consequently the semi-liquid food does not require lubrication. Just as the function of the mucus in the bronchial tubes is to keep these tubes clean, so the essential function of the oral mucus is to keep the mouth clean. Mucus is a liquid, tenacious and ropy in its nature, which under certain circumstances clings to hard substances. Chemically, perhaps, its best-known characteristic is that it forms a flocculent precipitate when treated with acids. These properties of mucus are well known. The following quotation from the work of Professor W. E. Gies and his collaborator, Dr. Lothrop, will indicate some further characteristics:

"Mucin occurs in saliva, and apparently also on dental surfaces, primarily as acid salts in concentrated colloidal solution. When viscid mucinous coatings are treated with basic material, such as carbonate of an alkali or an earthy element, the mucin mass becomes superficially more smeary and slippery by reason of the production of more soluble mucin salts at the surface. Complete mechanical removal of a mucin plaque from a tooth is facilitated by the addition of a basic material that renders the mucin superficially more viscous, but the slippery surface thus produced may make the application of considerable friction necessary for the detachment of the plaque. On the other hand, when a viscid mucinous deposit is treated with acid material, the mucin mass is completely disintegrated by a curdling or agglutinative process, the particles are devoid of adhesiveness to smooth surfaces, stickiness disappears because of the precipitation of caseous mucin itself, and the entire disorganized mass may be readily flushed away."

A consideration of these properties of mucus leads us to the conclusion that it is quite ingeniously suited for keeping the mouth free from the undue lodgement of food particles, when the foods are not converted by artificial means into some bland pap-like form which stultifies efficient mastication, negatives "considerable friction," and precludes the possibility of its being disintegrated so that it may be readily flushed away. It matters but little whether the chemical reaction of the food is neutral or alkaline, for during the mastication of food the saliva becomes alkaline if in its resting state it is acid, and the slippery state of the mucous coating on the teeth (and gums) is assured, while the ropiness of the mucus is left unimpaired.

On the other hand, if the food is more acid than can be neutralized by the copious flow of alkaline saliva, which it stimulates, the mucous films themselves are disintegrated and easily removed by the saliva and mucus after the acid has been swallowed. Thus, then, the mucus has not only the power of facilitating the removal of food particles and shreds which have been disintegrated by mastication, but it has also, under certain dietetic conditions, the property of being disintegrated and carrying its own disintegrated self away. Under unsatisfactory dietetic conditions—that is, when the food is habitually alkaline and so soft as not to stimulate mastication—the mucous coating on the teeth may remain too long, stagnate, and become infiltrated with the salts of the saliva; that is to say, tartar may be formed; or, if the food is of a carbohydrate nature and of a sticky character, it may be rapidly converted into lactic acid by bacteria, decalcification of the enamel may take place, and dental caries may be initiated. Should, however, the mucus not be saturated with carbohydrates of an impermeable and easily fermentable nature, the bacteria of the mouth slowly disintegrate the mucous coatings on the teeth and facilitate its removal on those surfaces of the teeth where it has not been removed by disintegration or considerable friction. It is quite possible, too, that the ptyalin in the saliva may digest the carbohydrate radical in the mucus, just as trypsin does. Why, otherwise, should we have a saliva rich in ptyalin poured out when sugar is taken in the mouth?

When we consider these facts we see that mucus is ingeniously devised for oral hygiene, and it is not devised for the lubrication of the bolus of food to facilitate its transmission to the stomach, nor is it devised, as has been suggested, to keep the numerous boluses of food in the stomach from the action of the hydrochloric acid, so that the ptyalin may have a chance of converting the starch in the boluses. Indeed, it seems much more probable that the thorough incorporation of food with mucus facilitates the penetration of the hydrochloric acid throughout the whole of the contents of the stomach after a meal, and possibly this is one of the reasons why a meal of such a physical consistency as demands mastication is more quickly and satisfactorily digested than a meal of a similar nature which has been reduced to a pap-like form before it is taken into the mouth.

Saliva.

It seems to me more than probable that physiologists will require to reconsider their teachings with regard to the function of the saliva. Hitherto they have looked upon it as the first of the digestive juices, and the salivary glands have been regarded as the first of the digestive glands. Some physiologists realize that the digestion of starch is not the function of the saliva; at least Professor Noël Paton considers that its more important function is mechanical (to facilitate speaking, eating, etc.). I shall try to indicate what the function of the saliva really is, but if we have not discovered the function of the saliva surely the sooner physiologists set about discovering it the better. For quite a number of years I have studied physiological problems because of their importance with regard to human welfare, and have come to the conclusion that to all intents and purposes the saliva is not a digestive juice, but that it is practically wholly for the purposes of oral hygiene. The older physiologists based their ideas on the fact that ptyalin has the power of converting cooked starch into achrodextrine and maltose. But many questions arise which would appear to throw considerable doubt upon regarding this as the chief function of saliva. That the digestion of uncooked starch is practically negligible is admitted by them; indeed, we are told that ptyalin does not digest uncooked starch (Halliburton, F. A. Bainbridge and J. Ackworth Menzies). If this be so, we may ask why ptyalin exists in the saliva of animals at all? Is it conceded that the saliva is not a digestive juice in animals? Again, it has never been contended that ptyalin digests sugar, but sugar stimulates a relatively violent flow of saliva rich in ptyalin. Why, too, should ptyalin exist in the saliva from birth, as we are told by some physiologists? Oral hygiene is no doubt necessary with a milk diet, but are we to believe that ptyalin is there to digest starch which normally is not present?

Again, why is starch, immediately it has been masticated and mixed with the saliva, transferred at once to the stomach, where the conditions are so frequently such that the digestion of starch by the ptyalin is immediately arrested, or if it is not immediately arrested, it soon becomes so? Physiologists have, of course, long recognized this supposed delinquency of Nature, and attempts have been made to explain how ptyalin may have some reasonable time to digest starch before the contents of the stomach become sufficiently acid to arrest the action of ptyalin. Thus, for example, some physiologists (Bainbridge and Menzies) say: "The food, after a meal is taken, forms a compact mass in the stomach, and the hydrochloric acid of the gastric juice penetrates comparatively slowly into this mass." It is only, of course, a pure supposition to say that the food forms a compact mass in the stomach; nevertheless, they evidently imagine not only that the food passes down the oesophagus in bolus form, but that the various boluses become one glorified bolus in the stomach.

It is significant that these physiologists never seem to refer to the fact that the contents of the stomach may be acid from the very beginning of a meal. A meal may commence with acid *hors d'oeuvre*, the bit of fish which follows may be served with lemon juice, meat may be eaten with salad well seasoned with vinegar, and stewed or raw fruit or both may complete the meal with a further supply of acid, while acid mineral or alcoholic beverages, which are sometimes supposed to stimulate digestion, may, and very frequently do, accompany the meal at various stages. Nevertheless, I do not know that we are told

that acids taken in these ways interfere with the digestion except among dyspeptics. Indeed, Professor Pavlov, speaking of the reaction of the food, says: "It is apparent that acidity enjoys a special preference in the human taste. . . . These facts are all physiologically comprehensible when we know that an acid reaction is not only necessary for an efficient action of the peptic ferment, but is at the same time the strongest excitant of the pancreatic gland."

Another point on which there seems to be confusion is with regard to the medium most suitable for the digestion of starch. According to Bainbridge and Menzies, "the digestive action of ptyalin on starch is most energetic in a neutral medium." According to Foster, "the action of saliva on starch is favoured by a slightly alkaline medium." It is curious how this is always referred to as if the slight difference in the reaction of the saliva were really of considerable importance in digestion. I have frequently tested the reaction of saliva between meals, but certainly am unable to draw the inference that the liquefaction of starch is at all influenced in any practical way by the reaction of such saliva. On the other hand, the fact that the saliva becomes very distinctly alkaline when food is eaten, and for some considerable time after it is swallowed, seems to the older physiologists unworthy of being mentioned.

To us who think that oral hygiene should be at least as common in man as it is in animals, all these apparently confusing and inexplicable facts have a simple explanation. The marked alkalinity of the saliva when food is taken has a significance in that it is important that it should have that reaction while the mucus is specially required for removing food particles from the mouth. If the saliva were sufficiently acid the mucus could not function in this way. Moreover, the acids which so commonly accompany foods might decalcify the teeth. On the other hand, the reaction of the saliva between meals is of practically no importance at all, because the conversion of starch in the mouth into soluble starch proceeds to all intents and purposes sufficiently satisfactorily, whether the saliva be neutral or faintly acid, or faintly alkaline to litmus. It has been the subject of much contention, possibly on account of its lack of importance, whether acidity or alkalinity of the saliva was the more unfavourable to the inception of dental caries. The slight acidity of the saliva between meals may be important because of its favouring the liquefying rather than the acid-forming bacteria, but the greater power of an alkaline saliva in neutralizing acid formed by bacteria may at least equally help to prevent caries. The point is not settled.

Towards the beginning of this paper I suggested a use for the ptyalin when sugar is taken into the mouth, and to those who appreciate why sugar is liable to cause dental caries the reason for a copious flow of saliva when sugar is eaten is obvious. Similarly, the desirability of a copious flow of alkaline saliva when acids are taken into the mouth is equally obvious if we value the preservation of the teeth; but why an alkaline saliva should be thought desirable for digestion if acid is "necessary for the efficient action of the peptic ferment, and at the same time the strongest excitant of the pancreatic gland," I fail to see.

While we are regaled with the importance of ptyalin for the digestion of starch, little is told us of the functions of the salts in the saliva, but they, too, are obviously of importance from the point of view of oral hygiene and the preservation of the teeth. Dr. Joseph Head made the important observation that when the superficial layer of enamel of the teeth has been slightly softened by acid this enamel can be rehardened by immersion in saliva, and thus it would appear that the salts in the saliva have an important restorative value as well as being prophylactic in function with regard to dental caries.

The saliva contains something more—amoeboid phagocytic cells, the so-called salivary corpuscles. They may be regarded as the scavengers of the mouth, and, as far as we can surmise, their function is simply oral hygiene. We are told that they are probably derived from the tonsils (Halliburton), and, although we might expect that lymphoid cells derived from the tonsils would pass down the throat rather than come forward and mix with the saliva, I at least have not seen reference to any experiment or observations to excuse the idea that they come forward into the mouth. The late Professor G. V. Black

made a careful examination of the lymphatics surrounding the necks of the teeth, and refers to a portion of the connective tissue in immediate conjunction with the tooth, which is not covered by the epithelium, and says: "It seems to be through this space that the cells—the so-called salivary corpuscles found under the free border of the gingiva—pass." "These may be found at any time under the healthy gingivus, and their numbers are augmented with every irritation of the membrane."

It has always appeared to me that the only satisfactory method of controlling the bacteria in the sulcus between the gingival margin and the tooth is by means of these phagocytic corpuscles. If we admit that the salivary corpuscles exude primarily into this sulcus, we observe at once their importance in oral hygiene, and—in passing, it may be said—the value of masticating food of such a nature as will cause an irritation, or rather stimulation, of the periodontal membrane, and thus assure a sufficient supply of these scavengers and thereby prevent the onset of pyorrhoea.

All things considered, it appears that the function of the saliva is, *par excellence*, oral hygiene, and no matter whether the food passes into the mouth and down the oesophagus in the ordinary way or whether the food passes up from the stomach and out of the mouth, it may in general be said that the saliva is secreted in quality and quantity proportionate to the needs of the food, to expel the food as completely as possible from the mouth. I need hardly mention that although a copious flow of saliva is induced by vomiting, even physiologists of the old school could scarcely claim that under these circumstances the saliva was to be regarded as the first of the digestive juices.

I have put forward the preceding observations to induce physiologists to take up this subject, and to give an authoritative lead. For without this the rank and file of the medical profession cannot be expected to teach the public the new ideas with regard to oral hygiene consistently, and until the function of the saliva is properly taught the valuable work which has been and is being done by medical officers of health and health workers will have but little chance of achieving its beneficent results.

DISCUSSION.

Dr. DALE expressed his appreciation of the research which is being done by dentists upon the physiology of oral hygiene. Although physiologists (he continued) do not believe the zymolytic function of ptyalin as important as Dr. Sim Wallace supposes they do, yet in depriving ptyalin of any importance as an enzyme Dr. Sim Wallace leaves it with no definite function at all. In considering the origin of dental caries more importance should be attached to dietetic deficiencies in early life than to the cleansing action of saliva. Nor can the latter factor easily explain why some people never have to visit a dentist at all, whilst others, in spite of the utmost care, have to do so frequently.

Dr. CLARK remarked that if the function of the mucus in the saliva was only a cleansing one, it would be reasonable to expect that when sand was given to an animal instead of meat a higher proportion of mucus would be secreted in the saliva. Actually a more watery saliva is secreted. The same applies to the quality of saliva secreted in connexion with vomiting. It also contains more water instead of more mucus than normal saliva.

Dr. SIM WALLACE, in reply, said: My reason for not making reference to developmental deficiencies in my paper was that this has nothing to do with the physiology of oral hygiene. Moreover, oral hygiene is at least as important when there is hypoplasia of the enamel as when there is not. For other reasons the Mellanby experiments were hardly worth taking notice of. As far as I could gather the hypoplasia exhibited in these experiments must have been in existence before the special feeding of the puppies was commenced. The crown of a child's first permanent molar is formed five or six years before it erupts, and no doubt the crown of the corresponding tooth in a puppy is formed at least six months before eruption. If teeth show hypoplasia when they erupt, attention should be directed to conditions existing during the formation of

the crown, and not to the special feeding after the crowns are formed. The crown of a tooth does not grow after it erupts.

A relative lack of fat-soluble A in the food seems to have no effect whatever in causing dental caries. Thus it was found that during the war, when foods containing fat-soluble A—for example, cream, butter, milk, and meat—were very scarce or unobtainable, dental caries actually decreased. In Shropshire there was, indeed, a very remarkable decrease. Nor is there apparently any relationship between the prevalence of rickets and dental caries. In England about the same percentage of children have decayed teeth whether they have had rickets or not. In America and Australia, where rickets is extremely rare, dental caries is about as rampant as it is in England. There is no extraordinary difference in teeth with regard to resistance to dental caries. Any tooth, whether "good" or "bad," can easily be decalcified by lactic acid even when it is weaker than it frequently may be found under fermenting carbohydrates in the crevices of the teeth. The enamel, being lifeless, offers no active resistance whatever.

Often teeth with well-formed and thick enamel are specially liable to caries, simply because the thicker the enamel the deeper the crevices, and consequently the more liable to lodge carbohydrate. This is well exemplified in the upper later incisors, which never decay on the lingual aspect except when the enamel ridges are thick and form a pit or crevice on the lingual surface. Neither are there racial differences in resistance. The once excellent teeth of the Kaffirs have become about as bad as those of Europeans where they have been subjected to European food. Similarly with the Maoris and our own ancestors, both had excellent teeth.

The answer to the question of the use of the ptyalin is simply that it is there to liquefy any particles of starch which may become lodged in crevices or impacted between the teeth. When it has done this, so as to facilitate the flushing away of such starch, it has fulfilled its function of helping to secure oral hygiene. With regard to saliva being watery when sand is put into a dog's mouth, this does not run counter to anything I have said. If a watery saliva is effective in getting rid of the sand, there is no need for the saliva to contain much mucus.

THE CHEMOTHERAPY OF PYOGENIC INFECTIONS WITH SPECIAL REFERENCE TO THE ANTISEPTIC PROPERTIES OF ACRIDINE COMPOUNDS.*

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THE effects of operative and mechanical intervention and of specific immunization in the treatment of pyogenic infections are not sufficiently successful to discourage the attempt to secure additional aid from the use of chemical compounds. These may act either by stimulating the tissues of the host or by depressing the virulence of the infective organisms. There is no certain evidence that elevation of resistance can be effected by chemical means; on the other hand, many substances damage the vitality of bacteria. Hence the search for suitable antiseptics appears to offer a prospect of success. It has long been known, however, that the antiseptics commonly employed have little influence on organisms in contact with the tissues, since they act as general protoplasmic poisons, and are as a rule more harmful to the host than to the bacteria. Accordingly it is necessary to search for compounds with more desirable properties. Incidentally there is the com-

* The original work referred to here was mainly undertaken under the auspices of the Medical Research Council. The chemical portion of the investigation was carried out, in co-operation with Mr. R. Gaunt, in the Organic Chemical Laboratory, University of Leeds; the biological part was carried out in co-operation with Miss R. Gulbransen at the Bland-Sutton Institute, Middlesex Hospital, and the Pathological Department of the University and Western Infirmary, Glasgow; and special work was also done with Drs. W. Gilmour, E. L. Kennaway, and L. H. D. Thornton.

plex problem of determining what constitute desirable properties, as it is necessary to decide by relatively simple preliminary tests what substances should be subjected to therapeutic trial. It appears that one should aim at high antiseptic potency, especially under conditions as nearly as possible resembling those which may be met with in the body, together with low toxicity for mammalian tissues. Toxicity may be measured for the animal as a whole when the substance is injected subcutaneously or intravenously, and also for particular functions—for example, phagocytosis; and for special tissues—for example, epithelial membranes, such as the conjunctiva—by local application of the drug. These points may be illustrated by reference to the diamino-acridine compounds ("flavines"), which appear to be the most efficient antiseptics from the therapeutic standpoint so far investigated by us.

(We were indebted to Drs. Barger and Ewins of the Department of Biochemistry and Pharmacology of the Medical Research Committee for the preparation of acriflavine and proflavine.)

Antiseptic Potency.

The method usually adopted in defining the value of an antiseptic is to express its potency as the ratio of the reciprocals of the sterilizing concentrations of the substance in question and some standard compound, commonly phenol. In calculating this ratio the period of contact of the bacteria with the antiseptic is as a rule limited to a few minutes. Certain substances—for example, phenol and mercuric chloride—act rapidly; on the other hand, there are many powerfully antiseptic organic compounds, such as those of the diamino-acridine group and the di- and tri-aminotriphenylmethane derivatives (brilliant green, crystal violet, etc.), which cause death of organisms comparatively slowly; but, short of lethal action, they exert a powerful inhibitory or "bacteriostatic" effect. Hence it appeared that the antiseptic value of a substance intended for therapeutic purposes might be most suitably gauged by estimating its power of restraining growth and eventually causing death of the organisms, ample time being allowed for the latter result. Provided that the antiseptic is not neutralized in the tissues or that, if so, it can be frequently renewed, mere slowness of lethal action as determined *in vitro* matters little; the organisms will be controlled from the beginning.

Accordingly, fluid medium containing the antiseptic in varying concentration was inoculated with different types of bacteria, and after the mixtures had been kept for twenty-four to forty-eight hours at 37° C. the occurrence of proliferation was examined by noting whether turbidity had developed in the inoculated tubes as compared with the sterile controls, and also the number of viable organisms present was ascertained with sufficient accuracy by subculturing a loopful on solid medium. Thus effects short of total sterilization can be estimated; whereas by subculturing in fluid medium it is impossible to detect any degree of action short of complete sterilization. In addition to a watery solution containing a small amount of bacteriological peptone (0.7 per cent.), sterile ox serum, previously heated for several hours at 56° C., in order to destroy normal bactericidal power as well as accidental contaminating organisms, was employed.

Serum may be regarded as a highly suitable test medium. In virtue of its content in protein it has a powerful action in reducing the bactericidal effect of most strong antiseptics (for example, the potency of mercuric chloride is reduced one hundred times); at the same time it is very constant in composition and reaction, and it represents the fluid constituent which antiseptics in contact with the tissues are exposed to; for instance, in a surgically treated wound.

The test organisms commonly used were *Staphylococcus aureus* and *B. coli*; they represent types whose behaviour toward antiseptics is liable to differ markedly, a character which suggests a far-reaching difference in their biology. Experiments have shown that within wide limits the efficiency of the antiseptic as tested by the method described is practically independent of the size of the inoculum—for example, from 0.000025 to 0.1 c.cm. of recent peptone water culture per 1 c.cm. of medium. But inoculation with very large numbers of organisms should be avoided, as these fail to maintain themselves in the medium even in the absence of any antiseptic. Under the conditions of the test the sterilizing concentration of

diamino-acridine methochloride ("acriflavine"), as determined by the modal value obtained in an extensive series of experiments, is for *Staphylococcus aureus*, in peptone water 1 in 100,000, in serum 1 in 200,000; for *B. coli*, in peptone water 1 in 20,000, in serum 1 in 100,000. The striking result therefore appears that this substance is not reduced in its antiseptic power by serum. As regards the bactericidal action in watery medium, relatively small differences in hydrogen-ion concentration produce marked alterations in the activity of the antiseptic (see also Graham-Smith and Davis). Thus by altering the pH value of the medium from between 4 and 5 to 11 the sterilizing concentration for *B. coli* was lowered progressively from 1 in 2,000 to 1 in 200,000; the value for *Staphylococcus aureus* was affected similarly. As with other substances, so also in the case of the acridine compounds, organisms are met with which exhibit selective resistance—for example, certain atypical members of the *coli* group. It would appear, however, that such resistance is natural and not acquired, and that acquired resistance towards the dye, as recorded by Shiga in the case of *V. cholerae*, can only be slowly attained by staphylococcus or *B. coli*, and is not likely to be a serious factor in causing failure in treatment.

Methods of testing the antiseptic power of acriflavine by repeated inoculation of a mixture of dye and serum, and also by adding the antiseptic after growth of organisms (*B. coli*) had occurred in the medium, have shown that rapid exhaustion or deterioration of the antiseptic does not occur. The latter experiment resembles more closely than the others the condition met with in treating an infected wound. It has been found that a heavy growth of organisms is sterilized by the subsequent addition of the antiseptic with as great ease as are a few organisms added to the medium simultaneously with the antiseptic. A noteworthy fact is that in repeated tests carried out with a view to determining the sterilizing concentration, a certain amount of variability appears in the results. Similarly, irregularity in sterilizing action may occur in a series of tubes containing ascending doses of antiseptic. Thus occasionally concentrations of 1 in 130,000 and 1 in 40,000 may sterilize the mixture, while 1 in 100,000 fails. This observation corresponds with that recorded by Richet and Cardot on exaggerated variations in the amount of acid formed in different tubes of whey containing a constant concentration of certain antiseptics when all are inoculated similarly with a lactic organism. A possible explanation of such irregularity is that where lethal effects are slowly produced, as with the compounds here considered, there is a critical concentration in the vicinity of which the balance may be inclined in favour of the organism or of the antiseptic by factors which at present escape complete analysis. Diamino-acridine sulphate (proflavine) was found to be practically indistinguishable from the methochloride in antiseptic action. When red blood corpuscles, pus, or minced muscle (Fleming) are added to solutions of the dyes reduction in antiseptic power occurs; but Gay and Morrison have found that acriflavine is more actively bactericidal for streptococci when added *in vitro* to pus from experimental empyema in the rabbit than it is for the same organism in broth. In rabbits it is possible by means of intravenous injections of proflavine, which do not affect the health of the animal, to render the serum bactericidal for several hours when tested *in vitro* with *Staphylococcus aureus* and *B. coli*.

Toxicity.

When tested on the animal body as a whole, by subcutaneous injection, it is found that healthy mice of 20 grams weight will tolerate as a maximum dose 0.003 gram of proflavine (sulphate) and 0.0006 gram of acriflavine, whereas mercuric chloride is about ten times more toxic than the latter. In the case of rabbits 0.05 to 0.07 gram proflavine sulphate intravenously per kilo of body weight is well borne. As the result of an experiment on a monkey under an anaesthetic (A.C.E. mixture at first and later ether), for which we are indebted to Dr. Dale, it appeared that administration at a rate as great as 0.0025 gram per minute per kilogram of body weight caused some danger to the heart; under similar conditions this would mean that an average man weighing 60 kilograms should not receive an intravenous injection at a rate exceeding 50 c.cm. of a 1 in 330 solution per minute. (It is likely, however, that in the experiment the susceptibility of the heart was

increased by the anaesthetic.) Doses of 0.33 gram of proflavine sulphate in physiological saline have been given intravenously at this rate to adult subjects without untoward effects beyond transient sickness. The skin becomes stained of a yellow tint, which, however, completely disappears in the course of twenty-four to forty-eight hours. The dye is excreted by the kidneys, and, as estimated from the absorption spectra by Dr. S. Russ, fully a third of the amount administered can be accounted for in the urine passed during the subsequent two days. There is also excretion of the substance by the bile in the monkey.

Proceeding now to the action on cells and tissues, phagocytic experiments showed that with mercuric chloride, phenol, iodine, chlorine water, hypochlorites (in the form of "eusol" and Dakin's solution) and chloramine-T, the concentration which sufficed to kill bacteria approached closely to that which *in vitro* interfered seriously with phagocytosis; on the other hand, with acriflavine and proflavine several hundred times the bactericidal concentration was required before phagocytosis was inhibited. In this connexion recently reported experiments of Gay and Morrison are of much interest; using leucocytes (obtained from the peritoneal cavity of guinea-pigs after injecting broth) along with streptococcus culture and antistreptococcus serum, all incubated for two hours in the presence of varying amounts of acriflavine, they found that there was a range of concentrations from 1 in 6,400 to 1 in 128,000 in which the antiseptic had apparently not inhibited phagocytosis and had also sterilized the mixture. In the controls, containing serum without dye, the organisms, although phagocytosed, were not killed. With respect to the action on connective tissue in the human subject, there has been no evidence of any deleterious effect when a few cubic centimetres of 1 in 1,000 solution were injected subcutaneously. By contact with the exposed tissues in a wound the progress of formation of granulation tissue may after a time be interfered with, thus producing an inert surface covered by a fibrinous pellicle, as was first noted by Drummond and McNee. But the evidence points to this result being brought about by some auxiliary factors not yet precisely defined, possibly evaporation leading to concentration of the dye, as suggested by Pilcher and Hull. From the reports it would appear that the procedures of different surgeons may vary in details which can hardly be appreciated from written descriptions, and yet which are of decisive effect as regards their influence on wound healing. Thus it is a fact that large wounds may be treated with acriflavine solution (1 in 1,000) for weeks without disturbance in the development of granulation tissue or interference with epithelial ingrowth; this has been noted by Pilcher and Hull, and has been again recently demonstrated to one of the authors in a series of cases by Dr. Charles Bennett.

The attempt to correlate antiseptic action with toxic effects on connective tissue by means of tissue cultures *in vitro* has been made by Lambert. Mueller tested in this way the flavine compounds and a series of triphenylmethane dyes and found that the former were the only ones which did not require a greater concentration to inhibit streptococci than to inhibit tissue growth. It is noteworthy that in the case of brilliant green (tetraethyl-diaminotriphenylmethane sulphate), which has not been credited with the property of inhibiting growth of granulation tissue by clinical observers, five times as high a concentration was required to inhibit streptococci as to inhibit the tissue culture. Hence, as Mueller concludes, "it is altogether probable that in the body a greater resistance is shown by the cells, while bacteria, on the other hand, may offer less, as a result of even a moderate protective action on the part of the body against invading organisms." In view of the application of antiseptics to delicate epithelial surfaces, such as that of the urethra, it appeared important to attempt to estimate irritating properties. With this object several drops of varying concentrations were applied to the conjunctivae of rabbits, so as to keep the surface bathed for three minutes. The result was that the flavines, in relation to their antiseptic power, were very much less irritating than any of the other antiseptics already mentioned (concentrations of 1 in 150 of acriflavine and 1 in 50 of proflavine being generally tolerated without causing irritation), whereas the tolerated concentration of mercuric chloride lay between 1 in 250 and 1 in 500.

It is noteworthy that in the examination of a considerable number of commercial preparations of acriflavine no appreciable differences in antiseptic power have been detected, but certain specimens were definitely more irritating than the average. This property may be of considerable importance in relation to the treatment of gonorrhoeal urethritis; there does not seem to be any method of determining it other than the biological test. Blood coagulation is markedly retarded *in vitro*, as noted by Fleming, and confirmed by one of us with proflavine, as well as acriflavine, but no deleterious effects which can be ascribed to such action have been met with in the treatment of wounds. Red blood corpuscles—for example, of man or ox—suspended in 0.85 per cent. sodium chloride solution are actively agglutinated by acriflavine and lysed by proflavine, but when serum is present to the extent of 50 per cent. by volume a concentration of 1 in 750 of these substances has no such action.

To summarize the results relating to antiseptic power and toxicity, it may be said that the diamino-acridine compounds possess much more powerful bacteriostatic and bactericidal action in comparison with their toxicity for mammalian tissues than any other substances hitherto investigated. In addition, they are stable, and do not become inactive through undergoing chemical changes in the tissues. These, and certain other compounds referred to later, are the only powerful antiseptics which are not reduced in their activity by protein solutions such as serum.

Therapeutic Tests.

In the case of certain trypanosome and spirochaete diseases chemotherapeutic agents of so high potency are available that a single injection will cure an animal already moribund. It may be said at once that nothing approaching this has yet been found for bacterial infections. But experiments have shown that it is possible by means of antiseptics, other than Morgenroth's optoquin, to prevent the development of septicaemia in mice previously inoculated intraperitoneally with many times the fatal dose of virulent pneumococci. When dealing with an infection so rapidly invasive in character it is not surprising that the antiseptic must be introduced into the peritoneal cavity within a short period after the organisms. Obviously, the conditions are not adapted for demonstrating the special properties of a bacteriostatic agent; thus cures were obtained with phenol and corrosive sublimate as well as proflavine. Successful results were obtained only in a proportion of the experiments; but any positive results of this nature are important in view of the opinion so widely held that antiseptics only act detrimentally on the infected animal.

The fact that the antiseptic may prove effective without itself actually killing the organisms was seen in the case of an animal inoculated intraperitoneally with a mixture of proflavine and pneumococci; it survived and was examined after a month when a chronic peritonitis was found with abundant pneumococci on the surface of the liver. It seems reasonable to conclude that the antiseptic probably acts by reducing the numbers of viable organisms or their virulence, so as to adjust the balance in favour of the tissues. In the case of intraperitoneal infection with *V. cholerae* in guinea-pigs and mice, similar results have been obtained (Baumgarten). Many negative results have been recorded, as in the carefully planned experiments of Gay and Morrison, who failed to effect cure in streptococcal empyema of rabbits by intrapleural injections of acriflavine. It is to be remembered in this connexion that infections in animals seldom show the strictly localized character which is so common in the human subject; generalized infection is beyond the reach of a locally acting antiseptic, while, of course, toxæmia which has once developed cannot be influenced by purely antiseptic substances. However, an agent which fails to check generalized infection or to influence toxæmia is not therefore disqualified for use in local infections. But the estimates on which reliance must then be placed are mainly clinical, and these have shown an extreme divergence. Certain conclusions, however, may be drawn: (1) that in the hands of many surgeons the flavines when applied by relatively simple methods enable improved results to be obtained in the treatment of localized pyogenic infections; (2) that a similar value attaches to their use in acute gonorrhoea—Dr. David Watson reports (unpublished) that the statistical records of

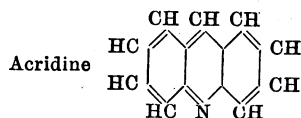
8,000 cases support his original estimate of acriflavine (see also Davis and Harrell); (3) that the flavines are of particular value in the prophylaxis of infection—that is, to prevent the occurrence of inflammation and suppuration, when applied shortly after the organisms have gained access to the tissues. Thus, cases of war wounds after excision and the application of flavine could be transported, with the probability that, although untouched in the interval, they would arrive at their destination without manifestations of infection or suppuration. This useful prophylactic action has been variously styled "cold storage" or "pickling" of wounds—terms which are unfortunate, inasmuch as they may imply that the beneficial effect is limited to this stage. It is of interest that various clinical observers have agreed that acriflavine is superior to proflavine in overcoming infection. Laboratory tests have not so far explained this difference. As regards attempts to influence generalized infection, it is scarcely to be expected that the transient antiseptic property conferred on the blood serum by an intravenous injection can have any decisive effect.

Urinary Antiseptics.

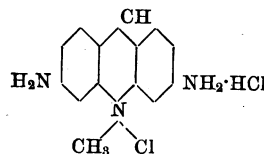
The fact that the flavines are excreted in the urine led to investigation of their possible value as urinary antiseptics. It was found independently by Davis and White and by ourselves that these substances acted best when the reaction was alkaline, and that antiseptic urine was excreted after an intravenous injection. Out of over two hundred aniline dyes investigated by Davis, White, and Rosen, only the two flavines, in addition to chloro-mercury fluorescein, caused the secretion of antiseptic urine after intravenous injection. The effect of proflavine administered in this fashion was tested in cases of *B. coli* pyelitis in children by Dr. Leonard Findlay (unpublished), who found a very definite effect in the form of diminution of pus and organisms in the urine for twenty-four hours following the injection; also the bacilli became long and filamentous; but no permanent result was obtained. More recently Davis has found that the urine in the human subject, provided it is alkaline, becomes antiseptic after the administration of the flavines by the mouth; this is probably the first time that such an effect has been attained by a drug.

The Relation between Chemical Constitution and Antiseptic Action in the Acridine Group.

Diamino-acridine methochloride had been prepared by Benda for Ehrlich and was named "tryptaflavin" on account of its powerful therapeutic properties in experimental trypanosome infections. We are not aware that its action on bacteria had been tested prior to our work, although Shiga published almost simultaneously results of his investigations on its action on *V. cholerae*. The parent substance is a compound of the following formula:



that is, a combination of two benzene rings and a pyridine. If the two side wings are removed, a pyridine nucleus remains; if only one wing is detached a quinoline nucleus results. It seemed possible that the antiseptic activity of acriflavine (diamino-acridine methochloride)



might reside either in the pyridine or quinoline nucleus reinforced by one or more amino groups; therefore, substances of this type were first prepared by one of us (J. B. C.). In addition, series of acridine derivatives were prepared and tested for their antiseptic power in order to determine if possible whether any law could be established relating chemical structure and antiseptic action within the group. Also, observations have been made upon phenazine compounds, on account of their close relationship to the acridine group.

Fragments of the Acridine Molecule.

The following were tested :

- α-aminopyridine hydrochloride.
- α-dimethyl-aminopyridine methiodide.
- quinoline hydrochloride.
- o- m- p- and α-aminquinoline hydrochloride and methochloride.
- 8-hydroxyquinoline sulphate, methochloride and methopicate.
- tetrahydroquinoline hydrochloride.
- methyltetrahydroquinoline methiodide.
- α and β-naphthoquinoline hydrochloride and methosulphate.
- tetrahydro- α and β-naphthoquinoline hydrochlorides.
- diamino β-naphthoquinoline and its methochloride.
- hydrochlorides of 1.4. and 1.5.naphtho-dipyridine.
- 1.1.dinaphthyl-2.2.imine.

The striking feature, in general, is the low grade of antiseptic power shown by these bodies. Thus, the hydrochlorides of quinoline, tetrahydroquinoline and the aminoquinolines, all failed to sterilize in dilutions exceeding 1 in 2,000, either in peptone water or in serum. The methochlorides of the aminoquinolines, except in the case of the ortho-compound, showed accentuation of antiseptic action in serum as compared with the hydrochlorides of the corresponding bases—a characteristic result which will be discussed when dealing with the acridine group. The hydrochlorides of α and β-naphthoquinoline were slightly more active than those of the bases already mentioned. No striking difference could be established between these and their tetrahydro-derivatives. Diamino-β-naphthoquinoline also showed no enhanced efficiency. The methosulphates of both naphthoquinolines and of diaminoquinoline showed intensified action in serum. The sulphate of 8-hydroxyquinoline, long known as an antiseptic under the name of "chinosol," is extremely active for *Staphylococcus aureus* (1 in 400,000 sterilized in peptone water and 1 in 100,000 in serum); this contrasts with the slight effect of hydroxy-acridine and aminoquinoline compounds. On the other hand, it is remarkable that the methochloride and methopicate of the base do not show enhanced action. 1.1. dinaphthyl-2.2.imine exhibits great discrepancy between its powerful action on staphylococcus and lack of effect on *B. coli*, which is similar to that exhibited by the triamino-triphenylmethane compounds, hexa-methyl and ethyl violet. But the most striking character of dinaphthyl-imine is the reduced effect in serum; thus 1 in 2,000,000 sterilized staphylococci in watery medium, but 1 in 1,000 failed to kill in serum. This is the most extreme reduction observed in the case of any substance, being twenty times greater than that effected by serum on mercuric chloride.

So far, therefore, it has not been possible to obtain fragments of the molecule which equal or even approximate closely to diaminoacridine in antiseptic properties.

Acridine Group.

The following were tested :

- Hydrochlorides and methochlorides (or in some cases methosulphates) of acridine.
- 9.phenylacridine.
- ✓ 3.6.dimethylacridine.
- 2.7.diaminoacridine (also the sulphate of this base).
- 2.7.diamino-3.6.dimethylacridine.
- 2.7.diamino-3.6.dimethyl-9.phenylacridine.
- 2.amino-3.methyl-9.phenyl-naphthacridine.
- 2.dimethylaminonaphthacridine.

The following general conclusions may be drawn from the results:

Action of the Amino Groups.

The introduction of amino-groups enhances the antiseptic potency both for *Staphylococcus aureus* and *B. coli*—for instance, acridine and diaminoacridine; dimethylacridine and diaminodimethylacridine. Thus the sterilizing concentrations of acridine hydrochloride for the two organisms respectively in peptone water are 1 in 2,000 and 1 in 1,000; in the case of diaminoacridine the figures are 1 in 200,000 and 1 in 20,000.

Effectiveness in Serum.

This is a characteristic of the compounds with unsubstituted amino-groups, and especially of the methochlorides of these bases. The further introduction into the diamino compounds of a phenyl group attached to the medial carbon atom, however, diminishes the action in

serum; this is exhibited both in the case of 2.7.diamino-3.6.dimethylacridine and 2.amino-3.methylnaphthacridine. On the other hand, the methochloride of 9.phenylacridine is much more active than that of acridine.

Comparison of the Antiseptic Power of the Methochloride and the Hydrochloride of the same Base.

The methochloride (or methosulphate, or methonitrate) is never less potent than the hydrochloride in the presence of serum, and in some cases the increased effectiveness shown by the methochloride is very remarkable—for example, in the case of 2.7.tetraethyl-diaminoacridine, 2.7.diamino-3.6.dimethyl-9.phenylacridine, 2.amino-3.methylnaphthacridine, and 2.dimethylaminonaphthacridine. Thus with the first of these bases 1 in 10,000 of the hydrochloride sterilizes staphylococci, while 1 in 400,000 is sufficient of the methochloride. In the case of the simplest member of the amino series, 2.7.diaminoacridine, and also where the substituents are directly attached to the outer rings, as in 2.7.diamino-3.6.dimethylacridine, the hydrochloride and the methochloride are practically equal in antiseptic power. It is noteworthy, however, that when the antiseptic power of diaminoacridine is diminished by substitution of ethyl radicals in the amino-groups, the enhanced action of the methochloride over the hydrochloride again becomes apparent. So far no rational explanation of the enhanced efficacy of the methochloride has suggested itself. The comparative effects of the hydrochloride and the methochloride of the same base in peptone water show a much less regular behaviour.

The hydrochlorides of certain of the compounds require the presence of a slight excess of hydrochloric acid in order to cause solution—for example, in the case of 9.phenylacridine and 2.amino-3.methylnaphthacridine; but the enhanced effect of the methochlorides over the respective hydrochlorides is not to be ascribed to the higher hydrogen ion concentration of the solution of the latter, since the addition of hydrochloric acid to the methochloride, so as to produce a solution of similar reaction, did not reduce the antiseptic power to that of the hydrochloride.

The Substitution of other Radicals for the Methyl Group in Diaminoacridine Methochloride.

The following were examined: Ethyl, propyl, n- and iso-butyl, iso-amyl, phenyl, benzyl, also the chloroacetate chloropropionate, and chloroacetanilide derivatives. The result was that within the limits of experimental variation these compounds are practically identical with the methochloride in their antiseptic power for both organisms.

The Substitution of Alkyls in the Amino Groups.

Tetramethyl- and tetraethyl-diaminoacridine were investigated. The tetramethyl hydrochloride, while practically equal to unsubstituted diaminoacridine in its action on *Staphylococcus aureus*, was distinctly inferior for *B. coli* both in peptone water and in serum. The tetraethyl compound was still weaker; thus with the latter the sterilizing concentration for *Staphylococcus aureus* in peptone water was 1 in 100,000 and in serum 1 in 10,000, while for *B. coli* a concentration not less than 1 in 1,000 was required. The methochloride and the methonitrate of the tetramethyl compound were practically equal to the hydrochloride; also, as in the case of the unsubstituted diaminoacridine, the effect in serum with the hydrochloride and the methochloride was practically equal. On the other hand, the methochloride and the methonitrate of the tetraethyl compound were much more active in serum than the hydrochloride.

Groups which Interfere with Antiseptic Action.

As has been seen, the introduction of methyl and ethyl groups into the amino radicals depresses rather than enhances the antiseptic potency, thus contrasting with the effect of similar substituents in the diamino- and the triamino-triphenyl-methane dyes. The substitution of one hydrogen atom in each of the amino groups by acetyl radicals practically abolishes the antiseptic action—for example, the sterilizing concentration of 2.7.diaminoacridine chloroacetate for *Staphylococcus aureus* in peptone water was 1 in 100,000 and in serum 1 in 200,000, and for *B. coli* in peptone water 1 in 20,000, and in serum 1 in 400,000; on the other hand, with the diacetyl-amino

derivative a concentration of 1 in 2,000 failed to sterilize. The carboxylic esters of 2.7.diamino-9.phenylacridine and of 2.7.tetramethyldiamino-9.phenylacridine were so weak as to indicate the marked depressing effect of the carboxyl group on the antiseptic property. The replacement of the amino groups by hydroxyls also led to practical abolition of antiseptic power, as is shown in the case of 2.7.dihydroxy-3.6.dimethylacridine, of which both the sodium salt and the methochloride were tested.

Comparative Efficiency for Staphylococcus aureus and B. coli.

Antiseptic potency for the two organisms does not invariably run parallel; thus the lethal concentration in serum for staphylococcus is 1 in 100,000, or higher in the case of 2.7.diaminoacridine hydrochloride (or sulphate) and methochloride and other analogous derivatives, 2.7.tetramethyldiaminoacridine hydrochloride and methochloride, 2.7.diamino-3.6.dimethylacridine hydrochloride and methochloride, 2.7.tetraethyldiaminoacridine methochloride, 2.7.diamino-3.6.dimethyl-9.phenylacridine methochloride, 2.amino-3.methylnaphthacridine methochloride. But in the case of *B. coli*, only the hydrochloride, methochloride and analogous derivatives of diaminoacridine and of diaminodimethylacridine and the methochloride of 2.amino-3.methylnaphthacridine reach this level of effectiveness.

Phenazine Series.

The following were tested:

Hydrochloride and methochloride (occasionally methiodide) of phenazine.

- 2.aminophenazine.
- 2.3.diaminophenazine.
- 2.dimethylamino-7.aminophenazine (methochloride only).
- 2.dimethylamino-6.methylphenazine.
- 2.7.tetramethyldiaminophenazine (hydrochloride only).
- 2.aminonaphthophenazine.

Also the methochlorides of 2.di-methylamino-7.amino-6.methylphenazine.

- 2.7.diamino-6.methylphenazine.
- 2.7.diamino-3.6.dimethylphenazine.
- 2.aminonaphtho-7.amino-3.methylphenazine.
- 2.methylamino-7.amino-3.6.dimethylphenazine, and methyl-tetrahydroquinoline-2.amino-3.methylphenazine.

The striking feature in this series is the relatively poor antiseptic power exhibited by the amino compounds in serum, especially for *B. coli*. The only compounds exactly comparable with the acridine series are those of the phenazine base, 2.7.tetramethyldiaminophenazine and 2.7.diamino-3.6.dimethylphenazine. The enhanced effect of the methochlorides as compared with the hydrochlorides of the same bases is evident in the phenazine series; but is not so striking as with certain of the diaminoacridine derivatives. The relatively greater efficiency of the methochloride of 2.dimethylamino-7.amino-6.methylphenazine as compared with 2.dimethylamino-7.amino-phenazine and of 2.7.diamino-3.6.dimethylphenazine as compared with 2.7.diamino-6.methylphenazine, suggests that methyl groups attached directly to the benzene rings may play a part in enhancing the antiseptic power in this series. For *Staphylococcus aureus* the methochlorides of 2.dimethylamino-7.amino-6.methylphenazine, 2.7.diamino-3.6.dimethylphenazine, and 2.aminonaphtho-7.amino-3.methylphenazine are powerful antiseptics, practically equal to the most potent of the acridine series; on the other hand, they are markedly inferior to the latter in their action on *B. coli*.

It cannot be said that the behaviour of the phenazine series throws any clear light on the antiseptic properties of the diaminoacridine group.

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SECTION OF OBSTETRICS AND GYNAECOLOGY.

Professor R. P. RANKEN LYLE, M.D., President.

DISCUSSION ON THE NEURASTHENIC ELEMENT IN MID-WIFERY AND GYNAECOLOGY.

OPENING PAPERS.

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I HAVE NO exact acquaintance with functional nervous disorders and would find difficulty in describing them, but I know that neurasthenia is defined as nerve exhaustion and that the disease is not limited to women. It is not difficult to recognize cases of acute neurasthenia, but they come under the care of the physician and not of the gynaecologist, though we may get a neurasthenic patient with some uterine trouble, and it may be that the uterine trouble is a factor in the production of the neurasthenia. These are not the cases that trouble us; it is the "neurotic" woman with gynaecological symptoms that is the problem, and that is the kind of case we have to discuss to-day. It is difficult to define the adjective "neurotic" as the cases vary greatly in degree, from the highly-strung woman who is entirely obsessed by her own ailments and who has only slight evidence of pelvic disorder, to the patient who has some definite lesion in the pelvis which causes more distress than it would in a woman with a healthy nervous system—or perhaps we may say more correctly, as one with a normal mental equilibrium.

As gynaecologists I think we see comparatively little of hysteria, although by its very name that is the disease which indicates uterine trouble. On the other hand, we see many neurotic women with gynaecological symptoms. In the early days of my professional life these cases seemed to be very common. I think that the methods of treatment were largely to blame. The patients were in the habit of paying frequent visits to the gynaecologist to have pessaries inserted and changed, to have speculums introduced, to have applications made to the interior of the uterus by means of probes, or to have the cervix treated by silver nitrate, or douched or swabbed with iodine or phenol. I think it is no exaggeration to say that many neurotics were manufactured in this way. At the present day, with different pathology and treatment, the number of cases which are neurotic is greatly diminished.

Women are generally thought to be specially liable to functional nervous troubles, but this is a point open to discussion. There are special periods when such troubles are most likely to be manifest: (1) during transition from girl to woman; (2) during menstruation; (3) in the course of pregnancy and parturition; and (4) at the menopause.

I have little to say about (1); it is the age of development, and emotional disturbance is not uncommon, but some of the special troubles at this time are due to failure of or faults in development. In the last three of the periods mentioned we certainly find disturbing influences from which males are free.

(2) The menstrual period in the average woman is not associated with any great nervous disturbance, although in some cases there may be a little instability of mind or temper manifest at that time.

(3) As regards pregnancy and parturition, it is a striking fact that most women are not much affected nervously by these conditions. During the war we have seen how the nervous strain inseparable from life in the danger zone affected many of our bravest men, yet the great majority of married women go through the trials and discomforts of repeated pregnancy and the pain and dangers of several confinements with the nervous system undisturbed. I believe that the neurasthenic element as a disturbing factor in parturition is negligible, but a difficult or badly managed confinement may result in chronic local diseases which may lead to secondary nervous symptoms. In pregnancy the nervous balance is sometimes disturbed, and many of the minor troubles, such as morning sickness,

frequent cough, salivation, etc., and even some of the serious diseases, such as pernicious vomiting, chorea, etc., may be due to this fact.

(4) At the menopause there is a great physical change which may be gradual but is often more or less sudden, and in some this is associated with much nervous disturbance. The local changes are also responsible for symptoms which may be attributed to neurosis.

These special circumstances which I have just mentioned have to be considered when we try to arrive at a just conclusion in regard to the special liability of the female, as compared with the male, to neurasthenic troubles. A discussion on these grounds only would not be very profitable. It is better for practical purposes that we should try to fix what may be called the reasonable symptoms of any local ailment. It may be of advantage to consider first the symptoms, as apart from the physical signs, of gynaecological ailments. They may be divided into subjective and objective.

SUBJECTIVE SYMPTOMS.

(a) Pain.

Pain is a common symptom, but of course varies greatly with the individual. The neurotic patient as a rule complains most, but her pains are apt to be widely spread or variable in location, and often in a situation where they are difficult to explain on an organic basis. If we are to believe the textbooks, the most common kind of pain is *backache*, which is generally regarded as a real symptom of disease of the pelvic organs. Unfortunately, *backache* is one of the common symptoms (if I am not mistaken) of neurasthenia. From the gynaecological point of view I am inclined to rate *backache* very low in the scale of importance. It occurs in chronic pelvic peritonitis with thickened and adherent appendages; it is also, in my experience, the common symptom in chronic cervical catarrh; but it is rarely mentioned spontaneously by the patient who has a displacement (prolapse or retroversion of a heavy uterus) or endometritis (so called) or chronic metritis. And yet these are ailments from which the majority of the patients suffer who come for advice to the out-patient department or consulting room. In these cases, if the patient is asked whether she has any pain, and if so where, she will nearly always indicate the lower abdomen, sometimes one iliac region, sometimes both, sometimes, but not often, the hypogastric region. If the patient complains mainly of her back we should suspect a neurasthenic element.

It has generally been taught that *iliac pain* is due to ovarian trouble. I believe that the ovary is about the only thing in that region that never causes it. Many ovaries have been needlessly sacrificed on account of this teaching, and when the pain is on the right side the patient may be considered fortunate if her healthy appendix is not removed by some eager but not very observant surgeon. Every woman who has a heavy uterus which is prolapsed or retroverted or in a position of what may be called exaggerated anteversion will tell you of this *iliac pain*. I do not pretend to explain it, although it seems reasonable to suppose that it is due to a mechanical dragging on the broad ligament. The pain is never acute, and is sometimes only present just before or during the first day of menstruation.

Periodic pain is generally of the nature of *dysmenorrhoea*. I have noted that with the menstrual function there may be some nervous disturbance apart from any local disease, but these cases are not numerous and not very striking. The *dysmenorrhoea* of the neurotic is never very convincing; the pain is not definitely localized; it is never intense and it is very variable, and it generally lasts during the whole of the period. This is very different from the acute disabling pain that attacks some young women. This is definitely located in one or other iliac region. It occurs nearly always in the first few hours of menstruation and then disappears. Mid-menstrual pain is almost certainly due to some local trouble, but its cause has not yet been definitely ascertained.

(b) Fatigue.

Many of our patients complain of being very easily tired, or always tired. This symptom, of course, may be due to some constitutional trouble such as faults of digestion, or it may be a purely nervous symptom. But there seems good reason to believe that some cases are due to a sort of

toxaemia. A striking example sometimes occurs in those cases of large fibroid tumour which diminish very rapidly after the menopause. This process is often attended by grave constitutional symptoms—rapid loss of flesh, changes in complexion, and digestive troubles. The results are often so striking that these cases may be diagnosed as malignant disease of the abdomen. I think this condition is produced in some way by the absorption of toxins from the rapidly disintegrating tumour. In fibroids in younger women the patient is often unduly tired, even when we allow for the weight of the large tumour and the effect of haemorrhage. The same symptom is common in cases in which the uterus is symmetrically enlarged by a chronic metritis. I think there are also conditions in the uterine mucosa and in the cervix which lead to a sort of toxaemia. It has often been stated that there is a relation between leucorrhoea and rheumatic troubles, and I have had cases which seem to prove that there is a distinct connexion between uterine catarrh and some skin eruptions.

(c) Tenderness.

When tenderness is caused by bimanual pressure on the uterus I think we may take it that there is some diseased condition of the uterus, if we can exclude a general hyperaesthesia of the skin. Cutaneous hyperaesthesia is not a common symptom of gynaecological trouble. Even in acute pelvic peritonitis there is not generally the same marked tenderness and boarding that one gets in acute appendicitis.

Under this heading we may consider cases of dyspareunia or vaginal spasm. This varies very greatly in degree. The worst cases are undoubtedly in women of very neurotic temperament. But in others the trouble is associated with a definite local lesion. I have no belief in abrasions of the vaginal orifice or fissures in the hymen as common causes, and have always found that dissection operations and the subsequent introduction of dilators have failed to relieve, except in some minor cases which would probably have improved without treatment. On the other hand, I believe that a leucorrhoeal discharge from the cervix or uterine cavity is often associated with dyspareunia. When I have found this to be the case it is my practice to curette the uterus, and this treatment I have found to give much better results than any cutting or stretching operation; it also answers in cases where there is a tender retroverted uterus.

If we consider the symptoms which we have just mentioned I think there are certain indications as to those which are due to a purely neurotic cause and those which are the result of some organic trouble. We find the key to the problem in the relation of symptoms to physical signs. I think that *backache*, in the absence of cervical catarrh and hypertrophy, or of pelvic peritonitis with thickened and adherent appendages (or possibly of an enlarged and retroverted uterus), is generally a purely neurotic symptom.

If the patient suffers from *iliac* or *hypogastric pain*, and if we find on bimanual examination that there is an advanced stage of prolapse or a heavy and enlarged uterus, either anteverted or retroverted, and if the pain is aggravated or only present just before or on the first day of the period, we are justified in deciding that the pain has a definite local cause and in treating it accordingly.

In *dysmenorrhoea*, if we find that the pain is definitely located in one or other iliac region (or in the hypogastrium); that it is very intense, but only lasts for a few hours at the beginning of menstruation; that the patient also gives a history of prolonged periods or of metrorrhagia or leucorrhoea; and if with these symptoms we find an infantile type of cervix and an acute flexion (ante- or retro-) of the body, the case may be removed from the purely neurotic category.

OBJECTIVE SYMPTOMS.

There are some other symptoms, commonly met with, in which the question arises whether they are indicative of organic mischief, or purely nervous.

(a) Bladder Troubles.

1. *Incontinence*.—The incontinence of young women is met with as a purely neurotic symptom, or at least as a symptom in which we are unable to find any local changes. These cases are nearly always amenable to moral treatment; removal to a nursing home or to a hospital is nearly always all that is required to cure them. Another class of

case occurs in middle-aged or elderly women who complain of inability to control the bladder. Some of these cases are due to cystocele; as the bladder and vaginal wall are very thin and the bladder lies at its lower part unsupported, any little pressure from below is sufficient to cause the urine to be expelled involuntarily. These cases can be cured by operative treatment. It is not necessary to refer to the incontinence which is due to fistulae or to over-distension of the bladder.

2. *Retention of Urine.*—This occurs as a nervous symptom after operation, and it is sometimes met with as a symptom of hysteria. We have to remember its occurrence in cases of gravid retroversion, and of impacted tumour in the pouch of Douglas.

3. *Increased Frequency of Micturition.*—This may be due to nervous causes or to inflammation or other disease of the bladder. We have especially to bear in mind that infection by the *Bacillus coli* is a common cause of frequency of micturition. Irritable bladder is quite common in women who suffer from gynaecological ailments. It is sometimes a symptom of a bad tear in the cervix which has involved the lower part of the broad ligament. As a result of this tear and consequent inflammation we find a firm scar or band which obliterates the lateral fornix, and pulls the cervix towards the affected side. The presence of this scar seems to limit (reflexly or otherwise) the capacity of the bladder. Division of the scar and a plastic operation will relieve the trouble. Another cause of frequent micturition is found in elderly women who are suffering from atrophic changes in the vagina, associated with senile vaginitis and sometimes with cystocele. This symptom may be very troublesome, but a diagnostic point is that the trouble occurs chiefly during the day-time, and the patient is not disturbed much at night. The condition of the urine will distinguish between cystitis and what may be called reflex bladder irritability. In cases where there is actual cystocele an operation may be required, but in other cases I have found that when sedative lotions used as a douche fail to relieve, the condition may be cured by a very thorough disinfection of the vagina under an anaesthetic.

(b) Irritation.

A similar method of treatment is very successful in some cases of *pruritus vulvae*. As itching and burning are subjective symptoms it may seem that this disease should have been dealt with in an earlier part of this introduction, but the redness, swelling, and excoriation of the external parts are very definite signs. Apart from those cases which are due to diabetes or parasites or leucoplakia, *pruritus vulvae* is generally regarded as a nervous disease, and it has been recommended that the nerves underlying the affected area should be divided. I have never found this necessary. In elderly women a vigorous disinfection, such as is usually undertaken after the patient is anaesthetized in operations on the vagina, is all that is required. In younger women, and especially if there is any sign of leucorrhoea or cervical catarrh, it is advisable to curette as well as to disinfect.

(c) Amenorrhoea.

Amenorrhoea is quite frequently produced by nervous causes; any mental shock or great anxiety may cause it. Perhaps the most common instance is the case of the unmarried woman who fears she is pregnant. The intense longing for a child on the part of a married woman may also bring about amenorrhoea. There is also the well-recognized group of cases in which scanty menstruation or amenorrhoea seems to be caused by deficient thyroid secretion.

(d) Phantom Tumour.

Very great distension of the abdomen may be a purely hysterical affection, but this can rarely give rise to any difficulty in diagnosis. A more common form of distension is that which is known as pseudocyesis or spurious pregnancy. It may appear before the menopause and when the periods are normal or only slightly diminished, but it is generally met with in patients who are passing through the menopause. Although these cases are now attributed to the influence of the ductless glands I think there is little doubt that there is also a nervous factor in their production. I think the same may be said of many other troubles of the menopause when these are exaggerated.

(e) Enteroptosis.

I have left this condition or group of symptoms till the end, as although it is generally considered to be one of the most common causes of neurasthenia in women it is not confined to women, nor is it a gynaecological symptom. It is true that with the descent of the abdominal contents we may have associated a prolapse of the pelvic floor or uterus, or a retroversion, but these are not outstanding features in the general clinical picture. As to the cause of the condition, I think it is open to doubt whether the origin of the trouble lies in the descent of the organs, or in the neurasthenic element, or in a general toxæmia. An investigation into its causation would be out of place here, but I may state that I am no believer in the mechanical theory of disease. Most of the abdominal organs may be displaced to an extreme degree without anything more than some inconvenience to the patient. I have seen cases in which an umbilical hernia reached half-way down a patient's thigh, and of prolapse of the uterus with complete eversion of the vagina, and in these the only complaints were a somewhat disagreeable dragging and a difficulty of locomotion or of sitting.

DIAGNOSIS.

I have little to add to what I have already said under the various divisions of the subject. I must emphasize again the point that the key to the problem as to how far the nervous element enters into a case is to be found in an accurate knowledge of the physical state of the pelvic organs. In the majority of cases this involves long practice in bimanual examination. Unless one is able to distinguish comparatively small differences in the size and general characteristics of the uterus and other pelvic organs, one is handicapped in coming to a decision.

What we have to decide in each case is: (1) Are the symptoms such as are generally found in a given lesion? (2) If the symptoms are exaggerated, is there reason to suppose that they will be relieved or removed by local treatment? or (3) Is the neurotic element so pronounced that local measures are likely to end in failure?

TREATMENT.

Because a patient is neurotic that is no reason why definite gynaecological troubles should not be treated. It may even be that the local trouble is the origin of the neurosis, or at least intensifies it.

1. Palliative.

Where palliative treatment alone is indicated, care must be taken that it is of a kind not liable to aggravate the nervous tendencies.

I think it would be well if treatment of patients in the out-patient room and consulting room were abolished. The passage of a speculum is unnecessary, except on the rarest of occasions, to anyone who has sufficiently developed the sense of touch. The uterine sound should never be used except during an operation. Applications to the cervix should be abandoned.

I have long ago regarded pessaries as nearly always useless and generally harmful. I know that there are women who think they cannot do without them, but I believe that nearly every case of this kind is merely an example of cure by faith. There are still some who seem to regard them as a panacea for all gynaecological troubles. If these cases be examined some curious conditions will be found. One finds them in cases of unreduced retroflexions, or of tumours or inflammatory swellings in the pouch of Douglas; Hodge pessaries where the uterus is anteverted; ring pessaries so small that they can do neither harm nor good, and pessaries in cases of senile vaginitis in which the patients have the feeling of prolapse but where no prolapse exists. Most of these patients have been educated into the habit, and I have found that most of them can be educated out of it. A woman who has a prolapse of a moderate degree is generally as comfortable without a pessary as with one.

Rest may be necessary where there is evidence of inflammatory trouble, or it may be advised as a general measure with overfeeding and massage for the neurasthenic condition, but many neurotic patients rest too much.

The use of a vaginal douche is advisable in some cases, such as those in which there is leucorrhoea accompanied by irritation; in these cases some sedative lotion may be

used, such as weak subacetate of lead. Hot douching every night is useful in cases of inflammatory exudation. Douching as a regular procedure where none of these conditions exists is probably harmful. The use of tampons, I think, has largely gone out, and I doubt whether they have any great curative effect.

Some gynaecologists get rid of responsibilities for a time by sending their patient to have a course of baths at some Continental or British spa. From a neurasthenic point of view this may be of some use; as regards the cure of any local pelvic ailment, except those which are due to some old inflammatory trouble, I think there is nothing to be said for it.

2. Operative.

The neurotic element must make us more guarded in our prognosis and more reluctant to operate. The objective symptoms of disease are a much safer guide here than subjective symptoms. In certain cases there can be no doubt as to the necessity for operation, however severe the neurotic element, such as in ovarian and most fibroid tumours, or pelvic inflammations. Where the local condition is one which is likely to affect the general health an operation is advisable. This will include cases of prolonged or profuse haemorrhage, of leucorrhoea, and cases in which a toxic element seems to be present. This class of case is fairly hopeful. The operations required for these conditions may be of a minor character, such as curetting, removal of a polypus, or excision of a catarrhal cervix, or they may involve an abdominal section with removal of ovaries and tubes or uterus. We may feel bound to give our patients the chance of better health in this way, but we must be prepared for a certain amount of disappointment.

The one class of case which I think is the least promising is that of a so-called displacement of the uterus—a case in which the uterus is retroverted but is not enlarged and in which there are no symptoms but back-ache. How many cases one has seen of women who have had this condition as part of a general enteroptosis, and who have had ventrofixation performed with no relief! I have known instances in which a kidney has been fixed, the uterus has been fixed, and, lastly, the colon has been fixed, and the last state of the patient was worse than the first.

A word must be said as to moral treatment. Many neurotics are amenable to the influence of a plain talk. Some of them have been frightened—or have been led to regard some slight ailment as a matter of great importance—and an emphatic reassurance may help a great deal. In very aggravated cases it may be necessary to explain to the patient that her troubles lie mainly in her own mind, or even to point out that she is wasting the best part of her life and is a burden to others, and that the cure rests with herself. It is not a pleasant duty or one which is likely to make the doctor popular with his patient—for the time at least—but I have known it to be effectual in some bad cases. It is especially successful in those in which an operation has been really advisable and has been performed. The period of convalescence is a favourable time to explain these things.

I have said nothing of psycho-analysis. I have my own impressions of this method of treatment, but have no experience of it. In any case it seems to be outside the sphere of the gynaecologist.

II.—E. FARQUHAR BUZZARD, M.A., M.D., F.R.C.P.Lond.,

Physician, St. Thomas's Hospital; Physician to Out-patients,
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DEPRESSION, insomnia, or disordered sleep, loss of energy loss of sense of proportion and of mental perspective indecision, irritability, or over-reaction to various forms of stimulation and restlessness, are the most important and most universal indications of the neurasthenic state.

But this picture of neurasthenia is far from being complete, and the canvas may exhibit features which by their prominence throw the common background into obscurity. The breakdown of organized control too frequently permits exuberant growth of certain elements in the patients' composition which have hitherto been kept in subjection, and which now manifest themselves in unmistakable fashion. Anxieties, fears, and obsessions, springing from foundations buried in the past, slowly or rapidly assume

proportions which gain for them the credit or discredit of being the primary causes of ill health. Moreover, these secondary eruptions frequently exhibit a physical bias and are projected in the form of pain, discomfort, or disturbance of function on one or other organ or region of the body.

Herein lies the difficulty of the gynaecologist, the surgeon, or the physician. The last may be confronted only with a mental disorder in the shape of a phobia, and may be in no doubt as to the method of treatment he should adopt; the first may be asked to deal with a pain or disorder of function referred to a pelvic organ, and may find the greatest difficulty in deciding whether the symptoms are primarily mental or primarily structural in origin. The answer to this question is often of great importance and mistakes in treatment may be of lasting effect.

From the gynaecologist's point of view it is obvious that he must satisfy himself as to the presence or absence of any structural defect to which pain or disorder of function can legitimately be ascribed. In the absence of such, or in cases of doubt, the question of neurasthenia may be raised, and he must be in a position to assess the likelihood of its presence. In other words, a correct diagnosis must precede and guide his treatment.

It is not sufficient to rely on a general statement or history to the effect that the patient is or is not neurotic, or on the presence or absence of an obvious source of worry or anxiety. Some of the most difficult cases of neurasthenia are those in which the patient has earned the reputation for not having a care in the world and for possessing a most equable temperament.

To arrive at a decision it is imperative not only to be familiar with the symptoms of neurasthenia, but to have some knowledge of the causes underlying this condition and its secondary manifestations. Before considering these in detail may I remind my audience that more than one factor is always concerned in the production of any morbid condition? It is usual for a bruise to follow a blow, but there are blows so slight that they only produce bruises in one person out of ten. That person is said to bruise easily, words implying a causative factor which operates in addition to the blow and which belongs to the individual. If this simple example of cause and effect is complicated by more than one factor we must not be surprised if we find a very large number of factors concerned in the production of neurasthenia. Anybody who is satisfied with one cause for neurasthenia, whether it be psychic, septic, static, or endocrinic, must inevitably come to grief in diagnosis and in treatment.

The first point to be studied in considering the etiology of neurasthenia is the inherent factor. As doctors, in our attempts to classify and pigeon-hole our patients we are apt to overlook individual differences. Go to a girls' school with a hundred pupils and you will not be surprised to find that each girl differs from her neighbour in form and feature; indeed, you would be surprised to find any two so alike that you could not distinguish them after a very short interview. Let us remember that the mental form and feature of each girl is equally if not more characteristic, that each responds in her own way to a common environment, and that in each the relative influence exercised by primitive instincts and desires is materially different. Let us recognize, too, that each girl is not equipped with the same amount of nervous energy even when allowance is made for transient conditions of health.

An appreciation of this last fact enables us to understand some of the early neurasthenic states met with in schoolgirls, in view of the fact that they are all put through a régime suitable only for the most robust. How often have we heard from the lips of a woman that while at school she never knew what it was to be tired! But public opinion at the school denounced manifestations of fatigue as reprehensible, and it was up to the exhausted individual either to be branded as a slacker or to assume a cheerfulness and vivacity which was purely fictitious. A third alternative, in the form of some hysterical disability or disorder of function, might provide a line of defence against the discomfort entailed by either of the other two courses.

A consideration of these factors in gynaecological problems at the period of puberty and adolescence may afford a clue to diagnosis and treatment. From a neurological point of view such a combination of factors, associated with a strong primitive instinct of acquisitive or sexual

character, may lead to disorders of conduct which may have disastrous results on the patient's whole life should the underlying and temporary causes escape recognition.

While insisting on the importance of realizing the inherent differences between individuals, I have intimated that fatigue—in itself a variable quality in regard to the amount of energy expenditure required to produce it—is a predominant factor in many neurasthenic conditions. Modern psychology, from which we have gained such invaluable knowledge in regard to mental mechanisms, has perhaps underrated the influence of fatigue in bringing about disorders of mind, and of rest in their treatment. This neglect represents the swing of the pendulum from the fashion of treating all functional disorders on the Weir Mitchell system, and so disregarding their other component factors. There can be little doubt that when a breakdown occurs in the compromise between social ideals and primitive instincts as the result of fatigue, rest may be sufficient in some cases to restore the balance, and in most cases it forms a necessary part of successful treatment.

From the gynaecological outlook the influence of fatigue and rest has many bearings. The intricate question of pain is not the least of these, and we must recognize the principle that visceral sensations normally giving rise to little, if any, disturbance of consciousness, and without any disagreeable tone, may assume painful qualities when the higher sensory centres have lost their healthy influence and authority. This principle is one to which we admit our adherence in ordinary good health when we acknowledge the exaggeration of some chronic pain in the presence of fatigue. In my belief there is no such thing as imaginary pain, but sensations may acquire a painful aspect when the higher centres are out of gear.

Fatigue is also closely concerned with sexual functions, and in women may manifest itself in precisely opposite ways. In a woman with a feeble sexual instinct the effect of fatigue may abolish desire altogether, and so create another factor in the evolution of a neurasthenic state. In another woman with strong sexual instincts fatigue, by interfering with the authority normally exercised by higher centres, leads to sexual misconduct of a kind which is regarded by the same individual in a healthy condition with abhorrence. Restoration of normal control may often be effected in such patients by rest alone.

But when we are dealing with the results of fatigue it is essential to find out whether there is more than one leakage by way of which nervous energy is being drained. The most common result of such investigation is to discover two factors which the patient regards as antagonistic or antidotal, but which in effect are cumulative. These two factors may be roughly described as fear and flight. The patient is beset by a conflict which she finds insoluble, and which she dare not face. Refuge from this dread is sought in distraction, often in frivolity, which in itself is a potent additional source of fatigue. The greater the exhaustion the firmer hold does the conflict obtain. Sleep is interfered with, and a complete breakdown is the result.

Many such patients must seek help from the gynaecologist on account of some pain or disorder of function, which in a healthy individual he would easily and successfully deal with. His intervention, however, whether operative or otherwise, has not the desired result, and unless prolonged and adequate rest, both mental and physical, can be obtained the patient's condition becomes worse rather than better. General and gynaecological surgery would show more successful results if every patient, before being submitted to a non-imperative operation, were carefully scrutinized from this neurological standpoint. I confess to having little patience with the surgeon who prides himself on the rapidity with which he gets his patient up after operation, or with the obstetric physician who lays down a time limit for rest after confinement regardless of what has gone before.

In considering the etiological factors concerned with neurasthenia reference must be made to the influence of age. Much importance has naturally been attached to changes which take place in the reproductive organs of women at the age of puberty and at or about the climacteric, and speculation has been rife in regard to the effects of these changes in the production of mental instability.

The conclusions generally arrived at can hardly, in the present state of our knowledge, be accepted without reserve, and the habit of attributing in an offhand manner

neurasthenic symptoms to the patient's age, as if there was nothing more to be said, is one to be deprecated. We must recollect that many individuals pass through the "dangerous ages" without exhibiting any signs of mental disturbance in spite of the change in their internal secretions, and we must not forget the psychic stress which so often operates at these periods of life. Reference has already been made to some of the difficulties which beset the schoolgirl, and these may be increased if the onset of puberty has found her unprepared by judicious education and enlightenment.

In my experience the large majority of adult women who exhibit symptoms of neurasthenia are between 35 and 45 years of age, and most of them have seen no signs of the approaching climacteric. It is at this period in a woman's life that mental stress is most apt to develop. Her energy is sapped by larger responsibilities, her place is being filled by younger women, and unless she is able to adapt herself to a new outlook on life she may find herself ill-equipped to face the years of declining power. The married and the single each have their own particular difficulties and anxieties, sufficient, as it seems to me, in most cases to account for the disorders of mental function which so often overtake them, without invoking the influence of glandular disturbances.

Civilized conventions have imposed on woman the necessity for greater repression than they have on man, with the result that we are often confronted with stories of many years of mental suffering quite unsuspected by friends or relatives. The strain of such years is apt to take its toll on the nervous system and to result in neurasthenic states which are quite unjustifiably ascribed to a physiological event.

It is more than likely that the menopause is a factor of some importance in a small proportion of patients, but I am not prepared to assess its value at the height it has attained in popular belief. Moreover, it has not been my experience to find a menopause artificially produced followed by neurasthenia in the absence of other more important factors.

The influence of age is so closely allied to that of the endocrine glands that a brief consideration of the latter, especially in relation to treatment, may not be out of place. I am hoping to hear in the course of this discussion the results of gynaecological and neurological experience in regard to the use of glandular preparations in the treatment of neurasthenia. They have been extensively used in men and women of all ages, and it would be interesting to discover the general opinion as to their efficacy. My own contribution to such a discussion can be stated very briefly. Beginning with an unfounded but enthusiastic bias in favour of their administration I have entirely failed to satisfy myself that they are of any therapeutic value in dealing with neurasthenia as such. There have, of course, been instances in which obvious thyroid inadequacy has been met successfully by the prescription of the appropriate gland, but I cannot recall a single case in which extracts of mammary, ovarian, or orchitic origin have indubitably exercised a curative effect. This statement must not be regarded as a condemnation of their use so much as a confession of ignorance as to how to use them.

Reverting to etiology, let me say a few words on what appears to be the most important factor in neurasthenia as it affects the patients of the obstetrician and gynaecologist. The instinct of self-preservation with its emotional counterpart of fear must certainly hold this place. Speaking generally, this instinct and this emotion are well developed in women from an early age, although they are not often brought into prominence in the everyday life of civilized communities. Moreover woman's fear of known dangers may not be more easily evoked than that of man. She is trained from an early age to repress fear in its relation to a number of more or less unknown contingencies. The fear of menstruation, the fear of sexual intercourse, the fear of child-bearing, the multiple fears associated with the responsibilities of maternity, and later on the fear of disease, of malignant disease, in connexion with the mammae and the pelvic organs. My experience amongst neurasthenic women leads me to believe that these fears, concealed from the eyes of the world, form a considerable part of the mental content of many so-called neurotic women, that they are based on unnecessary ignorance and lack of education, and that their dissipation would simplify to a large extent the work of the gynaecologist and

neurologist. Only recently I was consulted by an immaculate spinster of 47 years of age who had for months been nursing an agony of fear that she was about to give birth to a child, and on inquiry she was found to be entirely ignorant of the steps necessary before that fear could be realized. Such a story is hardly credible, but less improbable ignorance is constantly being exposed in consulting rooms.

But in proportion to the fears confessed, how many are never divulged except in the form of what one may term pelvic neurasthenia? It may justifiably be hoped that the emancipation and better education of women will result in the abolition of those phobias which depend on ignorance of physiology, but the terror of malignant disease seems likely to remain a curse to the peace of woman's mind for years to come.

The influence of fear concerns the gynaecologist in another way, in that it induces the nervous patient to conceal the early signs of disorder of function lest they may be pronounced to be evidence of disease. Thus does the instinct of self-preservation, lacking the guide of knowledge, defeat its own ends.

DISCUSSION.

Dr. BELL (Humshaugh) considered that some, at all events, and probably many, of the morbid nervous states of married women, were due to the impressions made on the nervous system by the fear of the pain of childbirth and its unaccustomed and unpleasant concomitants, and to the recollection afterwards, this being more marked in reticent natures. This fear and recollection could be abolished entirely by the use of scopolamine-morphine narcosis. So much was this the case that in succeeding pregnancies there was no fear of this kind, whereas, if neither chloroform nor scopolamine-morphine had been used, there was often terrified anticipation of approaching labour which produced very disastrous effects on the whole nervous system both then and afterwards.

Dr. WM. ROBINSON (Sunderland) looked forward to the day when neurasthenia would no longer be classed as a neurosis—to the time when the seat of the disease would be definitely located in some portion of the brain, just as paralysis agitans had been shown to be due to a visible progressive change in certain cells of the corpus striatum. At present most of the literature of neurasthenia was taken up with a medley of all sorts of weird symptoms referred to one or more organs of the body, due to loss or perversion of nerve control. It was not, however, to be expected that a marked change would be found in the nerve cells of the brain in a disease which might be temporary and curable; these changes might be abnormal biochemical reactions occurring, perhaps, as the result of the action of defective or excessive chemical messengers (hormones) carried to them in the blood stream from one or more of the ductless glands. It was impossible to imagine a function apart from a physical basis, and there was no system of the body in which function depended more upon structure than it did in the nervous system. Intelligence itself depended upon the number and development of the neurones in the four superficial layers (the plexiform and the three pyramidal cell layers) situated above the granular layer in the cortex of the brain, as was shown by their great development in man, and their late development in the individual and in the race. Instinct was a function of the three subgranular layers, and soon after birth these layers were developed to the extent of 82 per cent. (see Berry in BRITISH MEDICAL JOURNAL, July 16th, 1921, p. 72). The high development of the supragranular layers and the great size of the association areas surrounding the various special "centres" were the most prominent features of the human brain. Intelligence and fitness depended upon the number (and quality) of the neurones present at birth. Though they never multiplied, they and their connexions might be developed to a limited extent by education. Hysteria being an emotional disease, and its chief characteristic suggestibility (both as to cause and cure), was doubtless a disorder of these higher neurones; so was psychasthenia with its "phobias" and its hereditary character; but neurasthenia, being a chronic depression of various general functions of the body, was most probably a disorder of those subcortical centres which regulate the general economy. Thorburn classed ordinary acute shock (in which there was also an arrest of mental activity and

volition) as acute neurasthenia; and chronic neurasthenia as a condition of chronic shock. The predominating part (Dr. Robinson continued) that the sexual functions play in the body and the mind, especially in persons with defective control, accounts for the frequency with which neurasthenia is met by the gynaecologist. To get and to beget are the two strongest passions. The easily developed fatigue and prostration of the disorder suggest a likeness to Addison's disease and the possibility of its being due to deficient action of the suprarenal glands, especially when we remember that the other two chief symptoms of Addison's disease—pigmentation and vomiting—have never been produced by experiments on that gland and are most likely due to implication of the solar plexus, since they occasionally occur in chronic tuberculous peritonitis. The frequent vasomotor symptoms in neurasthenia show its intimate connexion with the sympathetic nervous system. We know that that system, acting through the splanchnics, can immediately produce those defensive responses in an animal when suddenly attacked and in great danger, which later are brought about by a flow of adrenaline, after the suprarenals have had time to act (Cannon). This is not surprising when we recollect that developmentally the medulla of the suprarenal is an offshoot of the autonomic system. The "phobias" and "anxieties" suggest some hyperthyroidism, symptoms of which are those occurring in fear and fright; and fear and fright are potent causes of neurasthenia. That the treatment of neurasthenia by organic extracts has been disappointing may be due to our ignorance as to the gland or glands required and the dosage necessary. The treatment of neurasthenia demands, as Osler stated, (1) a strong personality in the doctor or nurse; (2) certain means to be employed—a hospital, a home, an electric battery, a dominating suggestion, the correction or cure of some local (for example, pelvic) trouble, etc.; and (3) faith on the part of the patient—"only believe."

Dr. HELEN BOYLE (Brighton) confessed that she felt in a maze. Neurasthenia was such a vague term. Dr. Farquhar Buzzard's definition, "A disorder of mind wherein normal activities of life are difficult or impossible," made it almost all-embracing. She was impressed by two things: (1) By the very marked influence of the monthly period upon nervous and mental patients, usually, though not always, for ill. This had been questioned, but in her experience was incontrovertible. In the early stages of such conditions it was not uncommon for patients to develop suicidal tendencies, which completely disappeared when the period was over. This was misleading, as a cure might be postulated and a recurrence of the symptoms occur at the next period. (2) By the effect of lactation on the nervous mechanism. It was her experience that the stopping of lactation before the usual term of eight to nine months was likely to promote, not to hinder, the development of nervous symptoms. She thought that, unless it was otherwise impossible, lactation should be encouraged, not checked, in patients showing signs of nervous instability. She would like to know whether members of the Section had found excessive sex feeling to follow abdominal operations, and whether in such cases, in the absence of other indications, it was wise to have the abdomen explored for adhesions.

Mr. R. J. JOHNSTONE (Belfast) thought that neurasthenics might be divided into the hypochondriacs, who were usually people with too little to do, and the women who were suffering from the exhaustion produced by the bearing and rearing of a large family. He was in favour of ending the second stage of labour, especially in primiparae, as rapidly as possible, as many women after a long first confinement suffered from neurasthenia for a considerable time. He always impressed on patients after operation, especially after an abdominal operation, that they should not attempt to lead an ordinary working life for at least six months. He emphasized the importance of making certain, by operation if necessary, that no organic lesion existed which was really responsible for the symptoms of which the patient complained, and confessed that it was always with reluctance and a sense of failure that he finally arrived in any given case at a diagnosis of neurasthenia.

Dr. R. H. PARAMORE (Rugby) discussed the relation of the pressure within the abdomen to neurasthenia. He believed that neurasthenia was a condition affecting the

whole body. There was an enfeeblement of the brain (higher centres), of the systemic musculature, and of the viscera. The power of response of the brain depended on the nutritional state of the brain; and this nutritional state (apart from other factors) had resulted from the blood supply to the brain. The nutritional state of the brain was thus due, for one thing, to an adequately high aortic blood pressure—that was to say, to an adequate output of blood from the heart into the aorta per unit of time. But the output of blood per unit of time from the left ventricle depended on and varied with the supply of blood to the right auricle during the same time. Thus the nutritional state of the brain depended, for one thing, on the flow of blood to the heart. This blood reached the heart from three regions—from the skull, the limbs, and from the abdomen; but the skull was incompressible; the volume of the limbs varied but little from time to time; only in the abdomen did large variations in volume occur. If the musculature of the abdominal wall was persistently lax, as it often was in these cases, then disturbances in the vascular supply to the brain, and so of cerebration, were to be expected. The good effect of treatment by abdominal supports, rest, etc., the non-appearance of neurasthenia during pregnancy (indeed, the disappearance of neurasthenia in non-pregnant women when pregnancy ensued), and its easy rise in thin and worn-out people (especially its common occurrence in such women who had borne children), all indicated a relation between the intra-abdominal pressure and neurasthenia. Unlike Dr. Donald, Dr. Paramore believed many diseases were caused mechanically; and he believed that the mechanical failure of the abdominal wall and of the other associated musculatures to compress the abdominal visceral mass sufficiently was a cause, and he thought a potent cause, in the production of neurasthenia. The case referred to by Dr. Donald, in which a large fibroid gradually dwindled at the climacteric and the patient lost flesh and became neurasthenic, was, he thought, to be explained, at least in part, by the fall of intra-abdominal pressure rather than by the onset of a toxæmia induced by autolysis of the tumour, as Dr. Donald suggested.

Dr. MARY STURGE (Birmingham) urged the importance of restoring to their proper level in the body such displaced organs as the kidney and uterus, in order to eliminate an important factor in the cause and upkeep of neurasthenia. An experience of twenty-five years had profoundly impressed upon her mind the benefit that accrued to a nervous or even mental patient by relieving her of the strain produced by misplaced organs, if such existed. She related some typical illustrative cases. In one, a young woman, who became excited and almost suicidal at each menstrual period, the fixation of a loose kidney in its place was followed by rapid and permanent cure. In another case puerperal melancholia showed no signs of improving until the heavy retroflexed uterus was replaced; permanent recovery rapidly followed. She advocated care in the early reposition of displaced organs as a preventive of neurasthenia.

The President (Dr. RANKEN LYLE) said that the Committee of the Section had selected the subject for discussion because many patients suffering from exactly the same symptoms and physical signs received very different treatment, according to the way their cases were viewed by the practitioner or gynaecologist. He was not referring to cases of abdominal tumours, where the indication for operation was perfectly obvious and where little or no doubt could arise as to the proper method of treatment, but rather to a large class of cases where patients possessing some minor physical abnormality were at the same time suffering more or less from the general symptoms of neurasthenia. Twenty or thirty years ago all these cases fell into the hands of a person known as the gynaecological physician, who treated them by the insertion of various pessaries, and all sorts of minor treatment, such as applications to the cervix, tampons, douching, etc., and sometimes applications even to the interior of the uterus. This treatment resulted in the manufacture of a large number of chronic neurotics. A few years later, owing to steadily improving results obtained from operative treatment in general, this class of case gradually came under the notice of the operating surgeon or gynaecologist, who generally regarded the gynaecological physician with

great contempt, and in some instances went so far as to call him a "pessary monger"; but the operating surgeon himself was even more to blame, for he generally spent his time doing innumerable operations, such as Alexander-Adams's operation, ventrofixation and suspension, Gilliam's operation, trachelorrhaphy, and operations for the repair of minor lacerations of the perineum—operations which could not benefit the patient in any way whatsoever; the pretext for performing them was the false assumption that the minor physical abnormality found was the cause of the numerous neurasthenic symptoms of which the patient complained. What the Committee was anxious to ascertain was not so much the treatment of such cases, but the differential diagnosis and the relation, if any, between the mental or neurasthenic symptoms and the physical signs, so that patients of a typically neurasthenic character would not be subjected to unnecessary operations, and that the operative part of gynaecology would be reserved, as far as possible, only for those cases in which the benefit to the patient would be obvious and definite, and not of a purely speculative character. All, he thought, would agree that Dr. Donald had treated the subject in a masterly way, and had indicated many symptoms which were essentially of a neurasthenic character—some that might be either neurasthenic or have a physical basis, and others entirely due to physical causes. A point on which Dr. Lyle wished to insist was the great necessity for disbelieving all the objective symptoms complained of by a patient until they were verified by a careful examination. Patients often complained of all sorts of discharges, especially purulent discharges, when on examination nothing abnormal could be found. Other patients complained of uterine prolapse or displacements, or other conditions which had no existence in fact; the only explanation of these cases was a mental fear or dread lest they might perhaps develop. Dr. Buzzard's paper illustrated this fact—that many of the symptoms complained of by patients were due primarily to fear and dread, and he thus showed the absolute necessity of a thorough investigation in each case to determine the origin of such symptoms, whether due to fear or some departure from the mental or nervous equilibrium, or due to physical signs. Dr. Paramore mentioned increased intra-abdominal pressure, but this condition, apart from abdominal tumours, was essentially due to neurasthenia, and was associated with the neurotic bad habit known as "bearing down." This was the actual cause of the descent of the pelvic floor, producing such conditions as prolapse, procidentia, cystocele, and rectocele; the unsatisfactory results from operations in such conditions was due to the fact that their origin was more mental than physical.

Dr. FARQUHAR BUZZARD, in replying, thanked the members of the Section for their reception of his paper. He was sure that Dr. W. H. Paramore would have felt a glow of satisfaction if it could be asserted that pregnancy was never complicated by neurasthenia. This, unfortunately, was not the case, and if Dr. Paramore's theory were followed to its logical conclusion every woman after bearing a child should become neurasthenic and in the case twins become insane!

Memoranda:

MEDICAL, SURGICAL, OBSTETRICAL.

EXTRACTION OF PIN FROM RIGHT BRONCHUS IN A CHILD.

A GIRL aged 3 was referred to me by Dr. Jeffrey Ramsay of Blackburn, with the history that in the evening of May 18th, 1921, she had told her mother that she had swallowed a pin. She had been holding some pins between her teeth and one of these had slipped down her throat. There was no cough or difficulty in breathing, but x-ray examination was advised by Dr. Jeffrey Ramsay. Dr. F. W. Taylor reported the same evening that the radiogram showed a pin in the right bronchus, obliquely placed with the point on a level with the sixth costo-vertebral articulation and the head between the seventh and eighth ribs, about $\frac{3}{4}$ in. from the spine.

The following day, under chloroform anaesthesia at the Blackburn and East Lancashire Royal Infirmary, a 6 mm. Brüning's tube was passed into the right bronchus. This was replaced by an 8 mm. tube, as the smaller size did not give