want of progress. On all sides they are assured that the child is grossly mentally defective. It is only their perception that the visual and auditory memory of the child is relatively unimpaired that accounts for their steadfast refusal to believe it. Except in a few of the worst cases with microcephaly, and especially when there have been repeated convulsions, the mothers of these children have throughout maintained that the intelligence is good, and that, although they cannot speak, they understand every word that is said and that their memory is good.

In another way also the diplegic is apt to contrast with the child who is mentally defective. In spastic idiots the attention is weak, and cannot be fixed on anything. They touch many objects one after the other, but show none of that curiosity which is truly attentive. Their actions are inconclusive; they show no joy in the exercise of their powers or patience in practising them. It is striking to watch how differently in these respects the child who suffered from injury at birth may act. More and more he works with us in the attempt to overcome his disability. Though he cannot walk, if he is held upright he works his stiff little limbs with a will, laughing aloud with delight. Little by little, with infinite pains, he learns to grasp, to balance, to walk, and when, years later, he too achieves a degree of mobility and control the improvement is striking. It is just this power of auto-education which is conspicuously lacking in the imbecile or the idiot. In later childhood the progress is often so rapid that the mother, previously so despondent, eagerly expresses her satisfaction, while she is now able to convince others easily enough that the mental powers of the child are considerable.

It is in general only when the sensory and motor loss extends to and involves the hands that the confusion with primary mental defect arises. Those who are only paraplegic walk late and with difficulty, but are not thought to be idiots. They may be excitable and restless, because their helplessness leaves them too long in their mothers' arms, without sufficient outlet for their energies, but of their cleverness there is often no doubt whatever.*

But when the hands, all-important as they are for the auto-education of the infant, are insensitive and paretic, for the time being contact with environment is almost completely lost. Head⁹ has emphasized how extensive is the area of cortex which is devoted to the reception of sensations derived from the opposing surfaces of thumb and index finger. To the precision and complexity of the movements of the human hand, slowly acquired by the race in the course of ages, man owes his preservation and supremacy. And in the early months and years of life the infant, in its striving and progress, must recapitulate the story of its race. If it cannot, if the development of the hand is retarded, the avenue to the brain along which in normal infancy almost all the traffic passes is narrowed and obstructed. When there is added injury to the voluntary centres which control lips and tongue so that speech too is absent, the difficulties are still further increased. For speech is not only a means of expressing thought: speech clarifies thinking.

A long and close study of a group of some thirty of these cases--of all ages from earliest infancy to adolescence--has convinced us that they differ unmistakably from cases of primary mental defect with spasticity due to developmental causes. In a few frequent and persistent epileptiform convulsions have played havoc with the intelligence. After each convulsion the consequent deterioration in energy and achievement may be appreciable. But if convulsions are not present the defect commonly remains limited to a loss of voluntary movement and of sensation, involving a greater or a less extent of the body. The resulting retardation in development is most apparent in the first years of life, because

* It is very probable that Lord Byron's lameness was due to paraplegia as a result of a birth injury. Whatever its nature, it is clear at least that it was not due to a "club-foot." The lasts on which his boots were made are piously preserved in the Nottingham Museum, and they are symmetrical and well shaped. Mr. John Murray, of Albemarle Street, has been good enough to show me two surgical boots made for Byron as a boy. They show a long and slender foot. By a contemporary writer the poet is described as entering a room with a curious running movement, "running rather than walking." Again, "He moved with a peculiar sliding gait . . . in fact, with the gait of a person walking on the balls and toes of his feet." It is clear that the disability was much greater in early childhood, and was overcome to a considerable extent as he grew older. As a child he was taken to John Hunter, to Dr. Baillie, and many other doctors. Later he played cricket for Harrow, though with someone to run for him, and was a great swimmer. In other respects he was almost as well endowed: physically as mentally, of great strength and of amazing personal beauty. Again and again he refers to his lameness as caused by his mother's "false modesty at his birth." He suffered from repeated epileptiform convulsions.

education at that age proceeds by the refinement and analysis of sensation. The auditory and visual paths then are relatively unimportant. Gradually, by constant effort and with a success which varies with the extent of the original lesion, the child achieves in whole or in part that control of movement which comes so easily to the normal infant. From an early stage, however, those who know the children well can appreciate that despite the spastic limbs, the immobile face, or incoherent speech, the intelligence of the child is alert. Observation, memory, concentration of purpose, affection, intuition, and reasoning may be on a comparatively high level. No doubt the children are apt to be nervous and unstable. Like some caged animal, cut off from the stimulus of environment, they are apt to show strange traits--to have a capricious or unnatural appetite, to sleep badly, or to be unduly timid. These are drawbacks often perhaps inevitable, but with sheer mental defect they have nothing to do. In general it may be said that the response shown by these children to suitable education is remarkable. For them the methods elaborated by Dr. Montessori are especially applicable, and may give the happiest results. In later childhood, even when the voluntary movements remain very inco-ordinate, the mental powers may finally attain a very considerable development.

Conclusions.

1. Among cases of infantile diplegia or paraplegia it is possible to recognize a group in which the defect is confined to the sensorimotor cortical areas.
2. Probably all cases in this group are due to birth injury, although all cases of birth injury may not belong to the group.
3. Since education at first proceeds almost entirely by sensorimotor paths there is in early childhood a deceptive appearance of gross mental defect.
4. In later childhood progress may be rapid and recovery almost complete. The difficulty is overcome by the remarkable persistence in effort which is characteristic of most of these children. Even when voluntary movements remain stiff and awkward the child may be a quick learner by eye and ear. Inco-ordination may remain though character and intelligence may be on a high plane.

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THE MODIFICATION OF GASTRIC FUNCTION BY MEANS OF DRUGS.*

BY

T. IZOD BENNETT, M.D.,

ASSISTANT PHYSICIAN, MIDDLESEX HOSPITAL; ASSISTANT TO THE PROFESSOR OF PHYSIOLOGY, MIDDLESEX HOSPITAL; BEIT MEMORIAL FELLOW FOR MEDICAL RESEARCH.

(From the Department of Physiology, Middlesex Hospital.)

EVERYONE engaged in the practice of medicine is aware of the gulf separating the beliefs of the physician actively occupied in treating diseases and their symptoms, from the knowledge, precise but meagre, of the experimental pharmacologist. Whereas human hope and optimism have during many ages collected a series of remedies, often of unknown or varying composition, which may do good, the critical scientist, meticulously rejecting everything incapable of objective proof, has been unable to point to more than a very few substances which have definite organic actions, and has been obliged to condemn, as apparently inactive, large numbers of those agents which had previously been held to be of curative value.

In no branch of medicine is this contrast more apparent than in that which deals with disorders of the stomach; for medical writers, from the earliest times, have given enormous lists of remedies for such conditions, but it is with difficulty that the student can find, in any modern textbook of pharmacology, reference to drugs which can in any way modify gastric function. There has, indeed, until recent

* A paper read before the Section of Therapeutics and Pharmacology, Royal Society of Medicine, October, 1922. The expenses incurred in connexion with the researches have been partially defrayed by a Government grant made through the Royal Society.

years been so little experimental work carried on in connexion with the stomach that the reticence of the pharmacologists is natural, and the growth of knowledge in physiology has made clear so many errors in the reasoning of earlier writers that the discrepancy between traditional belief and proven facts is to a large extent explained. In this paper it is my endeavour to collect some recent experimental work concerning substances which can be demonstrated to affect gastric function; they can, I think, be best classified into (1) those whose chief action is on gastric secretion, and (2) those whose action is rather on gastric motility.

SUBSTANCES AFFECTING GASTRIC SECRETION.

1. Diminishing Gastric Secretion: Atropine.

For producing this effect we have an effective drug—namely, atropine. Very conflicting accounts have been published as to its gastric effects; thus Crohn¹ reports failure to produce any diminution in gastric acidity, whilst Bastedo² states that the atropine completely fails to affect hyperacidity and only checks acidity in hypersecretory cases in the period after the digestive stage is over. Other observers, notably Chiari,³ Mathieu,⁴ Schmidt,⁵ and Bergmann,⁶ speak highly of the inhibitory effects of this drug, and my own observations are in complete accord with this belief.

In Fig. 1 is seen the curve of free HCl obtained on fractional gastric analysis of a subject with a very free secretion of acid; the second curve shows the modification produced in this curve by the hypodermic injection of 1/100 grain of atropine sulphate. The effect is definite, and it must be observed that, the curve being obtained from analysis of gastric contents, it could not be expected that the atropine would affect the HCl which had already been poured into the stomach before the drug was administered.

But it is by oral administration of atropine or belladonna that the most marked effects can be produced. If the empty stomach be washed with a very weak solution of atropine even for a few moments, the fluid being then withdrawn, a marked inhibition of secretion is produced. Fig. 2 illustrates such a case, the heavy line being the subject's normal curve of gastric HCl, the broken line the curve subsequent to such a washing.

This is an experiment which I have many times repeated; it has been confirmed by Roberts,⁷ and it can be said that this local effect of atropine on the gastric mucosa is as definite as is the effect of the same drug when applied to the conjunctiva. It is probably because observers have chosen the hypodermic route that discordant results have been obtained.

Since performing these experiments it has become my custom in practice, when I desire to reduce gastric secretion, to administer atropine in small doses and in a large volume of water, the whole being given on an empty stomach.

2. Increasing Gastric Secretion.

For this purpose pilocarpine has somewhat naturally been recommended, and with certain precautions an increase can

actually be obtained. By washing the stomach with weak solutions I have sometimes succeeded in raising the curve of gastric HCl, as in Fig. 3, but usually, even when very small doses are applied, a local wash is absorbed, for the subject soon observes profuse salivation, and this saliva, if swallowed, will have a diluting effect on the stomach contents sufficient to reduce the acidity below its normal figure.

3. Substances Affecting the Gastric Secretion after its Evolution.

(a) Substances Neutralizing Acid Secretion.

In this group must be placed all the alkaline salts which have so long been used for the treatment of true or supposedly pathological excesses of gastric hydrochloric acid.

Following Pavlov, Bickel, Rosenblatt, and a score of others declared that such alkalis not only neutralized, but actually

arrested the secretion of HCl by the stomach. Du Mesnil, Bourget, von Leube, and others were, however, of opinion that the alkalis, and particularly sodium bicarbonate, were actual stimulants to gastric secretion, a belief which had the support of Claude Bernard⁸ himself. The fractional method of gastric analysis has enabled us to procure more

FIG. 2.—Showing effect on gastric secretion produced by washing the stomach with weak solution of atropine. Heavy line = subject's usual curve of HCl (fractional gastric analysis). Broken line = curve after preliminary wash with very weak solution of atropine.

definite evidence on this controversy than previously existed, and it has now been clearly shown that the effects of alkali administration are very much influenced by the time of administration.

In Fig. 4, for example, will be seen the normal curve of a healthy subject, and the curve from the same subject as influenced by giving sodium bicarbonate prior to a meal; it will be seen that during the period following the meal the alkali, rapidly neutralized, has led to an actual increase in the acid secretion.

In Fig. 5, on the other hand, is seen the effect of the administration of alkali at a later period; the acid already secreted is fully neutralized and a period of neutrality

lasting nearly an hour is followed by a rapid rise in the gastric acidity to its usual level. Magnesium hydroxide 12 grains and sodium citrate 5 grains were employed in this experiment.

In all such experiments it must be borne in mind that the gastric contents are not homogeneous, but the fractional method carefully

employed does give samples which offer a reasonable idea of the reaction of the total stomach content. In general, from the experiments of Crohn¹ and from my own observations, I feel that it may be said:

1. That sodium bicarbonate tends to excite the gastric mucosa to increased secretion, and that this effect more than counterbalances the neutralizing effect of the salt.

2. That other salts, particularly magnesium oxide, and bismuth oxycarbonate, have far less stimulating effect, and the former, weight for weight, possesses greater neutralizing power.

3. That the rational method of employment of these salts in cases of hyperacidity is to administer them at such periods after meals as will lead to their neutralizing

FIG. 1.—Showing effect on gastric secretion produced by hypodermic administration of atropine. Heavy line = subject's usual curve of HCl (fractional gastric analysis). Broken line = same after hypodermic injection of 1/100 grain atropine sulphate at point marked by arrow.

FIG. 3.—Showing effect on gastric secretion produced by washing the stomach with weak solution of pilocarpine. Heavy line = subject's usual curve of HCl (fractional gastric analysis). Broken line = curve after preliminary wash with weak solution of pilocarpine. Lowest line = more usual result, due to dilution of gastric content by saliva.

FIG. 4.—Showing increase in secretion of HCl produced by oral administration of sodium bicarbonate before meals. Heavy line = subject's normal curve. Broken line = curve when 120 grains of sodium bicarbonate had been given a quarter of an hour before meal.

effect coming into play without there being the possibility of producing any marked effect on the actual gastric cells.

4. That for producing inhibition of secretion reliance must be placed on drugs such as atropine and its derivatives.

5. That in gastric therapy sodium bicarbonate finds its greatest usefulness in those rather rare cases in which there is an excess of mucous secretion with low or absent hydrochloric acid.

FIG. 5.—Showing neutralizing effect of magnesium oxide given after meals. The broken line shows complete neutralization, lasting three-quarters of an hour, produced by giving 12 g. ains of magnesium oxide.

(b) *Substances Replacing Deficient Acid Secretion: Hydrochloric Acid.*

In cases where the gastric secretion of HCl is deficient or absent it has long been customary to give HCl by mouth; the practice is justified both on logical grounds and by the results obtained, but it is of interest to consider what the mechanism may be by which the result is obtained. In the first place it must be recognized that in order to obtain a concentration of HCl anywhere near that seen in the normal subject very large amounts of the acid must be administered to patients with achlorhydria. Thus, if the volume of a meal be reckoned approximately to be about one pint, it is necessary to give nearly two drachms of the B.P. dilute acid in order to raise the concentration of that amount of water to 0.1 per cent. HCl, and as all normal meals contain protein, which readily absorbs HCl, a great deal more than that quantity must be given if a serious effort is being made to increase the acidity of the gastric contents.

These considerations apply to cases of achylia gastrica, for it is doubtful whether the administration of HCl to cases of mere hypochlorhydria has any effect at all. Boldyreff,⁹ and more recently Rehfuß,¹⁰ have shown that in normal subjects any artificial increase in the HCl of the stomach contents is followed by a compensatory regurgitation of alkali from the duodenum, which quickly restores the acidity to its normal level.

It is, then, difficult to believe that the small doses of HCl usually given in cases of achlorhydria can have any but a psychic effect; but given more rationally there can be no doubt that striking results are often obtained, particularly in cases of achylia with diarrhoea. An interesting case was recently reported¹¹ in which a doctor with severe chronic diarrhoea and anaemia was apparently cured by such means; in this case the physician administered as much as half a litre of 0.5 per cent. HCl to the patient daily, introducing the acid by means of a gastric tube. One is unable to accept this case as a proven one of Addison's anaemia—the blood picture was not conclusive; but that a striking cure of an almost desperate case was secured is beyond dispute. My experience with HCl in pernicious anaemia is less encouraging; I have often produced temporary improvement in the intestinal symptoms, but never obtained evidence of anything suggesting cure. In a recent case—a particularly severe one with little sign of regeneration—I gave as much as half a pint of 0.5 per cent. HCl daily to the patient without apparently arresting the disease in any way. It should be added that this case had no diarrhoea, and further that no trouble was experienced in giving the acid by mouth, it being sucked through a tube in order to protect the teeth.

When one comes to inquire critically as to the true effects of the HCl secreted by the stomach, one is obliged to say that in general its functions are not essential to the organism. Thus its hydrolytic effects on protein can be replaced by the action of enzymes in the small intestine; its effect on the closure of the pyloric sphincter, if definite, is not the only means of closing that valve; again, even if HCl does normally bring about pancreatic secretion on its entrance into the duodenum, it is certain that achlorhydric subjects have usually a perfectly normal secretion of pancreatic juice.

Two effects predominate, the first being that on pyloric closure. There is no doubt but that such cases of achylia gastrica, and especially those with pernicious anaemia, have rapidly emptying stomachs, and the addition of HCl slows down this process. The second great function of HCl would appear to be its antiseptic action, and here again its oral administration in cases of achylia is, I believe, fully justified. I have here a flask which contains fluid removed from the fasting stomach of a patient with duodenal ulcer; the concentration of HCl in this case was very great, being that of decinormal acid. You will observe that though this juice has now stood exposed to the air for six months it is quite odourless, and no microbial growth has occurred in it. Similar samples from achlorhydric cases are foul-smelling in the course of a day or two.

A NOTE ON THE BITTERS.

This section would be incomplete without reference to the bitters, a series of preparations which have long enjoyed high repute in gastric medication. Textbooks have at times attributed to the bitters an effect in stimulating gastric secretion; later they have been said merely to increase appetite, and still more recently it has been said that their effect is actually *nil*.

The most complete recent study is by Carlson¹²; he showed that in the fasting state the bitters have no effect upon the hunger contractions of the stomach, and further that no definite influence on gastric secretion could be demonstrated. His observations were largely obtained from a human subject in whom complete stenosis of the oesophagus had been relieved by the establishment of a permanent gastrostomy. This young man, who was otherwise in perfect health, made it his custom to chew up his food in the normal way, and then to inject it into his stomach by means of a syringe. Carlson made observations on the amount and quality of the juice which could readily be extracted from this subject's stomach, and in a series of experiments with bitters he measured the juice after the mouth had been washed out with gentian, quassia, columba, and other drugs. He was unable to obtain any evidence of an increase in gastric secretion, nor did this subject observe any increase in appetite.

Carlson made a further series of observations on patients with loss of appetite; it was found that though the patients often said that their appetite had been improved by these medicines, measurement of their food consumption showed an increase of little more than 2 oz. in the amount eaten at each meal.

Making observations on the gastric secretion by means of the modified Einhorn tube, I have never been able to secure any definite increase in secretion by giving the subjects bitters as a preliminary mouth-wash; in several cases there has been an apparent decrease in HCl secretion, an effect which I believe is due to the somewhat profuse salivation sometimes caused. As in the case of pilocarpine, such saliva, if swallowed, will tend to dilute the gastric contents, and so diminish acidity.

It must, then, be concluded that we have no evidence of any marked effect on gastric function produced by the bitters, but there should, I think, be added the rider that, in fatigued states, the alcohol in which the bitters of the commonly used *apéritifs* are dissolved often removes from the subject unpleasant fatigue symptoms which may be a serious factor in inhibiting appetite, and possibly digestion also. Put in cruder terms, it is probable that a whisky and soda, or the army rum ration, is as effective an aid to appetite and digestion as is the more conventional cocktail, or sherry and bitters, or the less attractive condurango or quassia water.

DRUGS AFFECTING GASTRIC MOTILITY.

1. *Atropine.*

In the work to which I have already referred I found that in addition to its inhibitory action on secretion, there was evidence that atropine delayed gastric emptying. The effect was, however, not marked; whether by its hypodermic use or by its local application, the delay in emptying did not as a rule exceed a quarter of an hour with a test meal of the usual composition.

But it must be remembered that strong evidence exists showing that in cases of abnormal spasm of the gastric musculature the effect of atropine may be very marked. It has, indeed, become a matter of everyday radiographic practice to give large doses of this drug in order that the under-

lying cause of such spasms may be sought for. Thus it is no unusual thing for a patient with gastric ulcer to exhibit hour-glass constriction of the stomach on x-ray examination; if, however, he be re-examined after administration of full doses of atropine for three days, the constriction is seen to have disappeared, and the crater of an ulcer is often demonstrable. In cases of pylorospasm without discoverable organic lesion the patient's condition is sometimes remarkably improved by atropine treatment; one feels that such cases of disturbed gastric rhythm may to some degree be compared to those cases of auricular fibrillation with tachycardia which derive such striking benefit from the heart-block produced by the digitalis group.

2. *Pilocarpine.*

Fractional gastric analysis before and after lavage with pilocarpine demonstrates an increased rapidity of emptying after the use of this drug. The change is of a degree equivalent to the delay by atropine, and no really striking effect can be produced by doses which are within the limits of safety.

3. *Strychnine.*

This drug has long been given an important place in gastric therapeutics as a supposed means of increasing gastric motility.

An elaborate investigation recently published by an Italian observer, A. Berti,¹³ enables us to examine the question to-day from a better informed standpoint.

In addition to a considerable number of experiments on cats, Berti carried out a large series of observations on human beings, more than fifty subjects being employed, some of them being healthy students, others patients with viscerotaxis. All were examined under strict experimental conditions. At 8 a.m. an enema was given to secure complete evacuation of the colon; at 9 a.m. a test meal consisting of milky gruel containing barium and bismuth salts was swallowed, and x-ray observations of the stomach were then made half-hourly until the organ was empty. Two such observations were made on each subject, one with the plain meal, the other after administration of strychnine, several weeks being allowed to intervene between the two observations.

The strychnine was given in varying doses, both by mouth and hypodermically, with results which may be summarized as follows:

Nitrate of Strychnine given by Mouth.

(a) *Half-milligram.*—At first peristaltic movements were increased both in rapidity and depth and there was a marked diminution in the size of the pyloric antrum, evacuation of the stomach began sooner, and continued more rapidly than normal. Observed an hour later the peristaltic movements had lost much of their intensity, but the net effect of the drug had been to accelerate gastric emptying by more than half an hour. (Fig. 6, A.)

(b) *One Milligram.*—Again there was marked initial increase in peristaltic movement, but after an hour the contraction of the pars pylorica was sufficient to delay emptying, and, the peristaltic waves having become very feeble, there was on the whole a delay in the complete emptying of the stomach.

(c) *Two Milligrams.*—With this dosage the initial gastric movements were precipitate, there being a marked hypertonus of the pyloric region, violent peristaltic waves coming along the greater curvature, two or three being simultaneously visible, the whole producing a marked increase in the volume evacuated from the stomach in the first half-hour. But after the first hour these movements became feeble and feeble, hypertonus persisted, and the net effect was that there was considerable delay in complete gastric emptying. (Fig. 6, B.)

(d) *Three and Four Milligrams.*—The above phenomena were further accentuated; at first violent peristaltic waves coursed along to the pyloric region, where they often became arrested, forming an appearance suggestive of a string of sausages, or even contracting this portion to such an extent that the cardiac end of the stomach alone was visible. And again there was a rapid tiring

of these waves so that final evacuation was retarded, the stomach often emptying an hour later than the normal. (Figs. 6, C, and 7.)

(e) *Five or Six Milligrams.*—Here was seen the final expression of these phenomena, an initial rapidity of emptying being followed by the production of an hour-glass appearance. The general hypertonus appeared to be so great as to prevent peristaltic movement, the final hour-glass appearance being due to an extreme persistent contraction similar to that often observed in cases of saddle-ulcer of the lesser curvature. (Fig. 6, D.)

Hypodermic Administration.

With this method of administration the above effects were produced with smaller doses, in general each hypodermic dose producing the effect of about double the quantity taken by mouth.

My own work with strychnine has been limited, but several observations which I have made tend to confirm these findings, and it must, I think, be concluded that to produce

any beneficial effect on gastric catony very small doses of strychnine must be employed. The effects of larger doses are of considerable interest in throwing light both on the physiology of the stomach and on the motor disturbances of chronic ulceration. They seem to demonstrate once more the essential difference which exists between the motor functions of the fundus and those

of the pyloric portion of the stomach, and they elucidate the phenomena by which spasmodic hour-glass constrictions are produced.

When speaking of the motor effects of atropine I drew attention to the power of this drug in controlling spasm; it would be an interesting experiment to see whether strychnine spasm of the stomach could be controlled in this way.

A NOTE ON ADRENALINE.

The use of this substance in gastric therapeutics is, as far as I am aware, confined to cases where it has been employed in the endeavour to check haemorrhage. It should, on theoretical grounds, be capable of affecting both gastric secretion and gastric motility if its action could be brought to bear on the sympathetic nerve fibres supplying the stomach.

In 1920 Venables and I¹⁴ were able to demonstrate the very marked gastric effects which can be produced by unpleasant psychic influences—the suggestion of nausea or of fear being sufficient to delay gastric emptying for a considerable time and to inhibit the secretion of acid. It has been the custom of many physiologists to explain such effects as being the result of an increased outpouring of the internal secretion of the adrenals into the blood stream, with consequent effects on local tissues supplied with sympathetic fibres.

With such ideas in mind, I have carried out a series of experiments on normal men. On each subject two observations were made—in one the stomach was washed with water and a test meal given after, in the other the stomach was washed with adrenaline in various strengths and the test meal given as before. I have been able to obtain no evidence of any gastric effect of adrenaline by this means, though I have used strengths of as much as 1 in 5, and

have used sufficient to ensure a washing of the greater part of the gastric mucosa.

In a second series of observations the substance was used hypodermically, water being used in the controls. Again I have failed to demonstrate any gastric effect, though various doses have been tried, and blood pressure and subjective effects have sometimes been demonstrable.

Whether the use of adrenaline in cases of haematemesis is wise is at present a matter of controversy; that it has any effect on gastric secretion or motility my present series of observations does not support.

It is probable that the future will produce much experi-

FIG. 6.—Showing the effect on gastric motility produced by strychnine. A, 0.5 milligram; B, 2 milligrams; C, 4 milligrams; D, 6 milligrams. (After Berti.)

FIG. 7.—Showing effect produced by administration of strychnine. A, 3 milligrams; B, 4 milligrams. (After Berti.)

mental work which will enable us to employ a greater variety of drugs with definite effects on gastric function; it has been my endeavour in this paper to show that we already have a limited series of such substances, and I feel that the selection of those with appropriate actions must lead to a steady improvement in gastric therapeutics.

I would in conclusion express my thanks to my colleagues and the students of the Middlesex Hospital, in whose physiological department all my recent experiments have been conducted, and on whose generous help I have always been dependent.

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THE TREATMENT OF KALA-AZAR BY "BAYER 205."

BY

WARRINGTON YORKE, M.D.,

PROFESSOR OF PARASITOLOGY, SCHOOL OF TROPICAL MEDICINE,
UNIVERSITY OF LIVERPOOL.

THE following case, in which the drug "Bayer 205" was used with success in the treatment of kala-azar, is worthy of record, more especially as the only case hitherto reported ended disastrously.

A lascar, aged 22, left Bengal, in apparently good health, at the end of July, 1922. He became ill on August 12th, and in September noticed a swelling in the abdomen. He was treated with quinine on board ship and also at Cape Town, but did not improve and steadily lost weight. On November 8th he was sent to the Liverpool School of Tropical Medicine as a case of malaria with enlarged liver and spleen. He was emaciated (weight 95½ lb.), the liver and spleen were considerably enlarged, the latter extending well below the umbilicus to within three fingerbreadths of the brim of the pelvis; the temperature was 100° F., and the pulse 90 to 100. Examination of the blood for malaria parasites was negative. A leucocyte count revealed marked leucopenia—2,000 leucocytes per cubic millimetre. On careful searching of a whole blood film a single *Leishmania* was found. The faeces were normal and negative, except for the presence of a few *Ascaris* eggs. On November 13th the weight was 94 lb. A few *Leishmania* were again found in the blood on November 15th, and a spleen puncture made the following day revealed the presence of the parasites in very large numbers. The blood gave a well marked formol-gel reaction, and the urine contained a faint trace of albumin.

It was decided to treat the patient with tartar emetic administered by the rectum; and from November 16th to 20th daily injections of 1 grain in half an ounce of water were given; from November 21st to 23rd the daily dose was increased to 2½ grains of tartar emetic. The temperature, which, except for a couple of rises to 100° F., had been normal until November 19th, commenced to rise on this date and continued to oscillate between 100° and 101° F.; the weight on November 23rd was 93 lb. No injections were given from November 24th to 26th, but on November 27th injections of 2½ grains were resumed and continued to December 20th. The temperature remained above normal, rising at times as high as 102° F., until December 2nd, when it again became normal and has since remained so. The weight, however, gradually decreased until December 17th, when it was only 88 lb. On December 11th the leucocyte count had increased to 5,000 per cubic millimetre, but on December 12th a few *Leishmania* were found in the peripheral blood.

From November 16th to December 20th the patient had received by the rectum a total of 105 grains of tartar emetic; the injections, which were only half an ounce in volume, were well retained, and that some antimony at least was absorbed there is no doubt, as the urine examined on November 21st, and on subsequent occasions, was found to contain very definite quantities of the drug.

From December 21st to 27th no treatment was given. A spleen puncture made on the latter date revealed the presence of *Leishmania* in considerable numbers, but, so far as one could judge, not in such great numbers as on the occasion of the previous puncture on November 16th. On December 23rd the weight was 91 lb., an increase of 3 lb. during the week.

Whilst, therefore, there is some evidence that the intra-rectal course of tartar emetic had been beneficial to the patient, and had possibly to some extent reduced the mass of the infection, and perhaps might have resulted in still further benefit had it been continued, it is obvious that it

had by no means cured the disease. Under its influence the temperature had returned to normal, the general condition of the patient had improved, the leucocyte count had risen, and the parasites in the spleen had apparently become less numerous; but, on the other hand, the weight had continued to fall, the spleen and liver had not decreased in size, and parasites had disappeared neither from the peripheral blood nor from the spleen.

It was then determined to ascertain the effect of "Bayer 205" on this disease. The formula of the drug, which is a preparation of the German chemical firm Messrs. Friedr. Bayer and Co. of Elberfeld, has not yet been disclosed. It has recently been used with great success in the treatment of trypanosomiasis of man and stock. It has also been tried in various other diseases of man and stock—namely, in malaria, recurrent fever, and general paralysis of man, and in the triplasmoses of domestic animals—but without any success.

So far as I am aware, the only occasion on which the drug has been used in kala-azar is the case recently recorded by Mollow (1922). In this case only a very small dose (0.2 gram) was given, but the result was disastrous, the patient quickly developing alarming symptoms—severe rigors, headache, haemorrhages from nose and gums, severe vomiting which later became haemorrhagic, and collapse; later the patient became violently delirious, and finally death occurred sixteen hours after the injection. In view of this record the treatment of the present case by "Bayer 205" was undertaken with some little trepidation.

On December 23th an intravenous injection of 0.25 gram of "Bayer 205" was given. This injection, which in Mollow's case had rapidly proved fatal, produced not the slightest effect in the present case; the temperature remained normal, and the patient complained of no unusual sensation. On December 30th the weight had increased to 93 lb., and a second intravenous injection of 0.5 gram of "Bayer 205" was given; this likewise was attended by no ill effect—the temperature remained unchanged, the patient complained of nothing, and the urine remained normal. On January 2nd it was noticed that the spleen had shrunk perceptibly, and a third injection of 1 gram of the drug was then given, and again no reaction was observed. On the following day the weight was 96 lb. On January 5th it was noticed that the spleen had further decreased considerably in size; a final injection of 1 gram of the drug was given on this date, and, as on the previous occasion, was unattended by any rise of temperature or other sign of reaction. By January 8th the spleen had shrunk at least two inches, and was well above the umbilicus. On January 13th the weight was 101 lb., and the spleen had shrunk still further; a trace of albumin was found in the urine. On January 20th a spleen puncture was made, but no parasites were found; the weight was 103 lb. On January 28th another spleen puncture was made, and this was also negative; the spleen had decreased in size to such a degree that it now extended only about 1½ inches below the costal margin, and a somewhat comparable though less obvious decrease in size of the liver was also noted; the formol-gel reaction was still positive, the urine no longer contained albumin, and the weight had increased to 105 lb. The patient sailed for India apparently in excellent health on January 30th.

The history of this case suggests that "Bayer 205" has a very definite and rapid action in kala-azar. The injection of the drug was followed by no ill effect; the spleen rapidly decreased in size, as did also the liver, though to a less obvious extent; the general condition of the patient improved, he rapidly gained in weight, putting on 14 lb. within a month, and two spleen punctures, made respectively fifteen days and twenty-three days after the last injection of the drug, were both negative.

Possibly the violent and rapidly fatal symptoms observed in Mollow's case after the administration of so small a dose of the drug as 0.2 gram are to be explained, as the author suggests, on the ground that the patient was in an extremely poor condition at the time of the injection.

I am indebted to Messrs. Friedr. Bayer and Co. for kindly supplying me with a quantity of "Bayer 205" for trial.

REFERENCE.

Mollow, W. (1922): *Arch. f. Schiffs- u. Trop. Hyg.*, Bd. 26, H. 9.

A ROMAN Catholic Congress on the question of population will be held at Tilburg or Breda on April 12th and 13th, when the medical aspects of the question will be discussed by Professor Frans Daels of Ghent and Dr. A. W. Aussens of Utrecht.

DR. SOPHIE A. NORDHOFF-JUNG of Washington has founded an annual prize of 500 dollars, to bear her name, for the best work on the etiology, prophylaxis, and treatment of cancer. The judges will consist of members of the Munich Medical Faculty. The first award will be made at the end of this year.