RECTAL ABSORPTION IN CHILDHOOD

by

JOHN WILLIAM ALEXANDER MACKENZIE, M.B., Ch.B.

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C O N T E N T S

PREFACE

The work for this thesis was carried out in the wards and biochemical laboratory of the Royal Hospital for Sick Children, Glasgow.

Part of the investigation, comprising the absorption of glucose, sodium chloride and predigested protein from the rectum, has been prepared and submitted for publication under the title of "The Nutrient Enema".

I wish to express my gratitude to Professor Geoffrey B.Fleming for suggesting this research and for his constant help and encouragement in carrying it through. To Dr.H.E.C. Wilson, I am indebted for much assistance and advice.

This research would have been impossible without the co-operation of the sisters and nurses and to them I tender my warmest thanks.

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INTRODUCTION

THE ORIGINS OF RECTAL THERAPY

"A clyster is a noble remedie to dryve out superfluities of the guttes and of all the bodie, and it was found by a byrde called a Storke which to ease the pains of hir belly, was seen to put salte water with hir becke into hir hinder hole". So runs Gale's translation of John Vigo's account of the origin of the enema. This tale is probably a corruption of the ancient Egyptian fable which attributes the invention of the enema to the ibis. In the course of its toilet, this bird collects oil from the preen gland situated above the rump; it is likely that the legend was derived from the observation of this procedure.

As a remedy for constipation, the enema ranks among the oldest procedures in medical practice. References to its use are frequent throughout the whole of existing medical literature. In the Ebers Papyrus (B.C. 1500). perhaps the original medical treatise, prescriptions for enemata are given (Bryan, 1930). Herodotus, in the chronicles of his travels in Egypt. noted that it was then the custom for the natives to purge themselves for three days in every month by the use of emetics and enemata (Black, 1732). Hippocrates taught that enemata were to

be preferred to purgatives which should be given to none but very strong patients. Weak patients were given suppositories of honey and ox-gall (Hurst, 1919).

Although not as ancient as the simple enema, the nutrient enema is very old. It is not clear who the inventor was. The invention has been ascribed by different writers to Celsus, Galen and Avicenna. Of these three, Galen is the most probable. Nutrient enemata are definitely mentioned in his writings. On the other, although Celsus used such nutritive ingredients as honey in enemata, such enemata were evidently intended to be emollient and not nutrient. Indeed, he stated that enemata were contra-indicated in circumstances where they were likely to be retained (Lee, 1831). Avicenna, of course, practised at a much later period.

During the Middle Ages, the nutrient enema fell into disuse. Two of the English physicians of this period, John of Gaddesden and John of Arderne, although well aware of the value of the simple enema, apparently did not use the nutrient enema (Garrison, 1929, Cholmley, 1912).

According to Gros the nutrient enema was rediscovered by Abenzoar in the thirteenth century.

Ambroise Paré wrote of the nutrient enema as of an established procedure. He gave recipes for its preparation and rules for its administration. Chicken meat, milk, yolks of eggs,

decoctions of barley and wine were used. The bowel was to be well cleared out before the clyster was given, a large quantity was to be used so that all the intestines were filled and the patient was encouraged to sleep after taking the enema. Salt and honey were not to be used in the enemata because of their irritant qualities. At this time, as at present, some physicians did not consider the nutrient enema to be of value. Paré held the opposite view and in support of this view, he stressed the fact that he had seen patients who were unable to take food by mouth sustained by rectal feeding (Malgaigne, 1841).

In describing the treatment of wasting in infants, De Vallambert advised the use of nutrient enemata (Still, 1931). Bartholin and Peyer also believed this procedure to be of value.

In 1668, Regnier de Graaf published an authoritative work on the enema. To him, we owe the invention of the flexible tube for the enema syringe. De Graaf believed the nutrient enema to be merely of transient value but he recorded the prevailing theory of his time regarding the absorption of the nutrient enema. When prescribing a nutrient enema, the physician of these days directed that it should be given with more force than was usual in giving simple enemata so that it would pass through the large intestine to the small bowel where it was thought to be absorbed.

Ramazini (1633-1713) fed a girl suffering from paralysis of the oesophagus by means of nutrient enemata for

seventy days.

Thomas Sydenham used clysters in the treatment of many conditions. Many of the prescriptions that he gave included milk, sugar or eggs. Apparently these ingredients were not used for their nutritive value but rather for their emollient properties (Latham, 1848).

In the latter half of the nineteenth century, interest in the nutrient enema was heightened. The advances in chemistry allowed of the use of new methods in approaching the problem of rectal absorption. It was then customary to treat patients suffering from gastric ulcer by withholding all forms of food by mouth and instituting rectal feeding. Thus, the question of rectal absorption presented itself. Modern research dates from this period. Ewald, who was undoubtedly the leading clinician of this period in the investigation and treatment of gastric disease, believed the nutrient enema to be of definite value. At this time, when great advances were being made in understanding the processes of digestion, the question arose as to whether predigestion of the ingredients of the enema was necessary. Ewald did not consider predigestion essential and the recipe for the nutrient enema that he recommended was little different from that given by De Graaf.

When the mode of treating gastric ulcer changed, the more elaborate methods of rectal feeding fell into disuse and

nowadays rectal feeding is almost exclusively confined to the use of glucose and saline infusions. However, it is interesting to note that, as recently as 1936, Hutchison's "Food and the Principles of Dietetics" included prescriptions for such nutrient enemata as those recommended by Ewald and Boas.

The administration of drugs per rectum is as old a procedure as that of giving an enema. Prescriptions for suppositories as well as for enemata were found in the Ebers Papyrus. It would appear that these medicaments were intended to remedy constipation or for the treatment of local disease of the lower bowel. That the rectal route could be used for systemic medication is possibly an idea also of ancient origin. According to Stubbs and Bligh (1931), about 600 B.C., the Assyrians used opium suppositories as a remedy for abdominal pain. This method of administering drugs with the object of producing a remote effect does not appear to have been widely practised. Possibly, it was Cullen who rediscovered the value of the rectal channel in systemic medication. In describing the treatment of tetanus, he wrote that large quantities of opium should be employed before deglutition becomes difficult, "or that, if this opportunity be lost, the medicine, in sufficient quantity, and with due frequency, should be thrown into the body by clyster; which does not seem to have been hitherto often practised", (Thomson, 1827).

The Present Position: Since patients with gastric ulcer are no longer treated by fasting, the indications for artificial feeding are more limited and the nutrient enema is used more rarely. Modern opinion is sceptical of the value of enemata of an elaborate nature. The rectal infusion used nowadays seldom contains ingredients other than glucose and sodium chloride.

The importance of giving abundant fluid in many surgical conditions is now fully realised. In many cases, the quantity which can be taken by mouth is insufficient and requires to be supplemented by other means. Of these methods of administering fluids, the intravenous infusion has recently become very popular and tends to overshadow other extra-buccal methods of giving nutrient fluids. Although the value of the intravenous method, as a quick and sure means of providing fluid, is undoubted, one cannot deny that it also possesses disadvantages. It demands skill, an aseptic technique, specially prepared solutions and apparatus and, unless carefully supervised, dangers of overloading the circulation or of air embolism can arise from its use. On the other hand, rectal infusions are easily prepared and administered and there is little danger of overdosage. They are safer and less disturbing to the patient. From a statistical survey of cases receiving fluid after operation, Fantus (1936) has found that a greater diuresis followed the administration of enteral fluid. This was associated with a favourable prognosis.

It seems, then, that rectal infusions play a useful part in fluid replacement but at the moment no unanimity of opinion exists regarding their value as a vehicle for nutriment or salt. In view of this incomplete acceptance of the usefulness of the nutrient enema, the previous investigations are reviewed and studies with three of the more important substances used in nutrient enemata, namely glucose, normal saline and predigested protein are presented.

Nowadays, few nauseous concoctions of drugs are given by mouth. In many cases the pharmaceutical chemist has been able to eliminate irritant substances present in the impure drug. Where irritant properties are possessed by the active principle, devices such as the cachet are used. Thus, most drugs are given by mouth.

In special cases, however, other means of administering drugs are necessary. The oral route is contra-indicated in cases where the patient, from whatever cause, is unable to swallow. An inadequate quantity may be absorbed when persistent vomiting is present. Sometimes, when high dosage has to be maintained, the amount of drug given by mouth requires to be supplemented by other means.

The recognised methods of giving drugs apart from the oral route are by intravenous, intramuscular or subcutaneous injection and by rectal infusion or suppository. Of late years,

the administration of drugs by injection has increased greatly and, correspondingly, the rectal channel has declined in popularity. The parenteral injection of drugs affords a sure and swift means of supplementing or supplanting the oral administration of medicines, but the rectal method, particularly where there is no urgency, may still be of value. This may be true especially in the case of small children where the use of a needle is always to be deplored and if possible avoided, and where drugs with an objectionable taste or smell have to be given.

Recently, interest in the use of the rectal channel has been revived and a number of proprietary preparations for rectal use have been placed on the market. Extravagant claims have been made as to the utility of these preparations. For this reason it was thought that an investigation of the absorption of drugs given rectally would be of some practical value. Three drugs were chosen, potassium bromide as a simple salt which, foreign to the body, is excreted unchanged and is capable of relatively simple estimation, sodium salicylate as a more complex substance which when taken by mouth not infrequently produces gastric disturbances and which may be determined easily. Sulphanilamide was chosen as a still more complex drug which is widely used. A commercial preparation of sulphanilamide for rectal administration has lately been placed on the market and as the present preparations of this drug for injection are not entirely satisfactory

there is a definite need for an examination of its behaviour after rectal administration. This drug has the added merit that its determination in the body fluids is not elaborate.

The investigation was carried out with children recovering from various diseases. Care was taken that no case was used where the disease or the effect of drug treatment might interfere fortuitously with the metabolism. In the cases suffering from acute disease, it was not until the stage of recovery was firmly established and all drugs stopped that the observations were made. Where children suffering from chronic disease were used, it was only when they were symptomless and temperature, pulse and respirations and in the case of rheumatic infections, sedimentation rates were normal. The conditions that these subjects had suffered from were the following: acute rheumatism, chorea, valvular disease of the heart, erythema nodosum, epituberculosis, hilar tuberculosis, pleurisy with effusion, pneumonia, bronchiectasis, nephritis, hydronephrosis, pyuria, haematuria, bacilluria, osthostatic albuminuria, rheumatoid arthritis, pseudohypertrophic muscular dystrophy, spastic diplegia, oesophageal stenosis, convulsions, enteritis, purpura, exophthalmic goitre and hyperthyroidism.

This study was commenced since the outbreak of war and has been carried on during the last two and a half years. The number of cases has been limited by several factors. The exigencies of the War in respect of beds reserved for casualties

has had a marked effect on the number of available cases. As the hospital has been short staffed, this has also had its effect since the help of the nursing staff is so essential to this type of work. It was necessary to select cases able to co-operate and this factor excluded most children under the age of five years. As many of the observations entailed the collection of urine specimens, children whose habits were unreliable were not used. Most of the children co-operated very well, though a few had to be discarded as they refused to do so.

The investigation is set out in four parts, namely, the absorption of glucose, the absorption of sodium chloride, the absorption of predigested protein and the absorption of drugs.

A. THE ABSORPTION OF GLUCOSE

A great number of investigations on absorption of nutrient enemata have been devoted to the problem of absorption of rectal glucose but a perusal of the literature reveals a welter of results and conclusions.

There seems to be complete conflict of opinion regarding the changes, in fasting subjects, in the blood-sugar content following the injection of a glucose enema. In a series of 7 cases Tallerman (1920) found a rise in the peripheral blood sugar level in 4 cases and a fall in 3 cases. Varela and Rubino (1922) obtained a rise in only 3 out of 17 cases but in one case sugar was found in the urine after the enema. Although Levi (1927) found a rise in 11 out of his 16 cases, he did not consider this method of administering glucose of much value. Mekie and Miller (1929) reported equivocal results. In 1932 Julesz and Winkler found a rise in 12 cases in a series of 14; in the same year, Scott and Zweighaft were unable to demonstrate a rise in the blood-sugar level in any one of their 50 cases. Collens and Boas (1933) found a significant rise in the blood-sugar level in 24 normal subjects after rectal glucose. Von Tornack (1938) was unable to demonstrate an increase in the blood-sugar content after rectal glucose.

Many workers have found that rectal washouts, done at varying periods after the glucose enema was given, failed to yield more than a fraction of the glucose injected. Carpenter (1925) regarded this disappearance of glucose as signifying absorption. Pressman (1930) on the other hand believed that glucose not recovered was lost through fermentation; in one experiment he showed that when a 5 per cent. solution of glucose was incubated for 7 hours with a suspension of faeces, only 0.5 per cent. could be recovered.

In animal experiments, McNealy and Willems (1929:1931) and Davidson and Garry (1939) found that there was no loss of glucose from loops of colon in 1 hour and 1½ hours respectively. Ebeling (1933) confirmed these results but found that when dogs were rendered hypoglycaemic, 21 per cent. of the glucose was absorbed in 2 hours. All these animal experiments were carried out under anaesthesia and immediately after the abdomen had been opened. It is possible that the artificial conditions under which the experiments were performed had some influence on the results thus obtained although absorption was shown to take place from control loops of ileum under the same conditions. The experiments of Burget, Moore and Lloyd (1933) were planned to forestall this criticism. Loops of large bowel were constructed from the transverse colon and allowed to heal. Not till the animals had fully recovered from the operation was the absorption

of glucose investigated. These workers found that from 18 to 27 per cent. of the instilled glucose was absorbed from the loops of colon in 1 hour when a 10 per cent. solution of glucose was used. Colonic absorption took place at half the rate of that found when control loops of ileum were used.

Indirect methods have also been employed. The effect of glucose enemata on the respiratory exchange, on ketosis and on nitrogen metabolism have all been investigated. Here also, opinions are conflicting.

An increase in the respiratory quotient following rectal glucose, indicating utilisation of carbohydrate in the tissues, has been reported by Reach (1902), Bergmark (1915), Carpenter (1925) and Curry and Bargen (1935) in the human subject and by Fleming (1919) and Hari and von Halasz (1918) in animal experiments. Carpenter found that the respiratory quotient was increased by from 0.02 to 0.05 after glucose per rectum. Hari and von Halasz reported a case in which the respiratory quotient increased from 0.76 to 0.95. However, although this is a very striking increase, the value of the experiment is doubtful since it was performed under very artificial conditions.

The effect of glucose enemata on ketosis has been investigated by a number of workers with varied results. Satta (1905) and Hubbard and Wilson (1922) thought that a reduction in the excretion of ketones was effected, but Langdon Brown (1911),

Mutch and Ryffel (1913) and Corkill (1936) were unable to confirm this.

In the course of their experiments on the effect of rectal glucose on ketosis, Bergmark and Mutch and Ryffel found a marked fall in the excretion of nitrogen after the glucose enema. The latter workers attributed this fall to the protein-sparing action of glucose absorbed from the enema and showed that the fall was approximately equivalent to that produced by a similar amount of glucose taken by mouth. Langdon Brown was unable to demonstrate this effect.

Little help in the elucidation of this problem has been offered by clinicians. Only two cases have been reported, one by Collens and Boas (1933) and one by Bauer and Monguio (1932), where glucose has been given per rectum in hypoglycaemic coma. The coma was relieved in both of these cases.

Summary of Literature: There is no conclusive evidence to show whether glucose is or is not absorbed from the "rectum".

In this investigation rectal absorption was studied in children between the ages of 5 and 13 years. The problem was approached in three ways. In one group of investigations the peripheral blood-sugar levels were observed after the rectal

injection of glucose solutions in the fasting subject. Secondly, in some of the cases just mentioned, the quantity of glucose recovered from a rectal washout at the end of the test period was determined. In the third group of investigations, the effect of rectal glucose on the nitrogen metabolism was studied.

Blood-Sugar Studies.

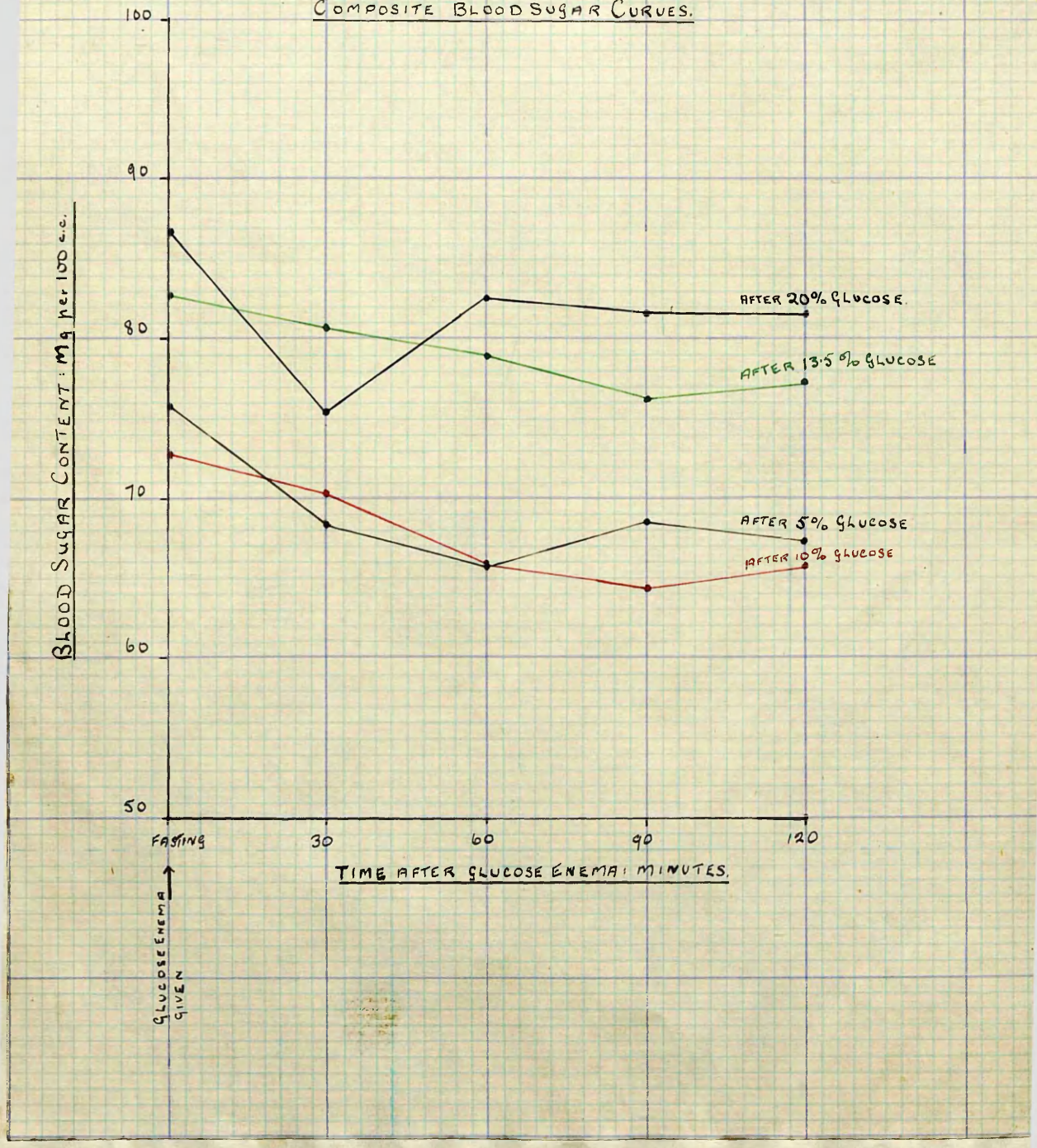
The fasting subject was given a cleansing enema one hour before the start of the observation period when a specimen of capillary blood was obtained from the ear or the finger. The glucose solution was then allowed to run into the lower bowel through a rubber catheter (No.8 English gauge) inserted into the rectum. In subsequent investigations all fluids administered rectally were given in this way. The enemata were all retained and did not give rise to discomfort except when 20 per cent. glucose solution was given. With these the subjects had difficulty in retaining the fluid and in a few cases colic was experienced. Further specimens of blood were taken 30, 60, 90 and 120 minutes after the enema was given. Five per cent. glucose in water was used in 10 cases, 10 per cent. in 10 cases, 13.5 per cent. in 11 cases and 20 per cent. in 5 cases. Trials were made with these concentrations for the following reasons:- 5 per cent. glucose in water is isotonic; 10 per cent. glucose is a strength commonly used for routine rectal injections; 13.5 per cent.

glucose was found by Auchinachie, McLeod and Magee (1930) to be the optimum concentration for absorption of glucose from the small bowel; 20 per cent. glucose was used because Tallerman (1920), Julesz and Winkler (1932), Franke and Wagner (1924) and others had found a rise in the peripheral blood-sugar content after the injection of a very concentrated solution. Since the 20 per cent. solution proved irritating, higher concentrations were not tried.

The changes in the blood-sugar levels are shown in Tables 1 to 4. From these it will be seen that, from a normal fasting level, there was a steady fall in the great majority of cases. A study of the blood-sugar levels determined at 30, 60, 90 and 120 minutes after the enema was given fails to reveal any significant deviation from the slow fall in the blood-sugar percentage. In fact, with one exception the blood-sugar content remained within the normal fasting limits in all cases throughout the test period. The single exception to this is Case 33. In this case alone, was a significant rise in the blood sugar noted. In the oral glucose tolerance test it is customary to give 1 gramme of glucose per kilogramme of body weight. In the first series, where a five per cent. glucose solution was used, this figure was not attained; thus, it may be said that the quantity of glucose given was not sufficient to produce a definite rise in the peripheral blood-sugar level. In the majority of the

BLOOD SUGAR STUDIES.

COMPOSITE BLOOD SUGAR CURVES.



later cases, however, at least 1 gramme of glucose per kilogramme of body weight was given and yet no rise in the blood sugar level resulted. There is no noteworthy difference between the readings obtained in the various series, indeed the strength of the solution does not seem to have affected the results materially. Composite curves have been constructed from each series and these are shown graphically in the accompanying table.

Since these negative results were obtained with 'normal' children, it was thought that any small potential rise in the blood-sugar level masked by the liver in the normal subject would possibly be demonstrated in a condition where there was carbohydrate intolerance. Accordingly, a case of hyperthyroidism was given glucose per rectum (1 g. per Kg. of body weight as a 20 per cent. solution in water). The resultant curve was compared with that obtained from an oral glucose tolerance test using a similar quantity of glucose. Table 5. Here again, a negative result was obtained but as can be seen from the oral test, there was no marked carbohydrate intolerance in this case.

If glucose is absorbed from the rectum in any quantity it seems likely that there will be a rise in the blood-sugar level as occurs when it is taken by mouth. On the other hand it is possible that the glucose is absorbed so slowly that the liver is able to store it and thus prevent its entrance into the general circulation. In view of the negative evidence obtained from the

above studies other means of attacking this problem were examined.

The Glucose Content of the Rectal Washout.

If glucose is not absorbed from an enema it should be possible to recover a large proportion of it by re-emptying the bowel.

In 15 cases the rectum was washed out at the end of the 2 hours test period and the washings examined for glucose. There was great variation in the amount of glucose recovered. As will be seen from Tables 1, 2 and 4, the percentage of the instilled glucose recovered varied from 7.45 to 60 per cent. Where 5 per cent. glucose in water was used, the average recovery was 30 per cent. (2 cases), with 10 per cent. glucose it was 28 per cent. (9 cases) and with 20 per cent. glucose it was 17.8 per cent. (4 cases).

It is impossible to say whether the loss of glucose represented by these figures was due to absorption from the bowel, to incomplete recovery of unabsorbed material, or to fermentation. There is, however, some evidence to show that neither fermentation nor loss of glucose due to incomplete recovery played an important part. In a carefully controlled study on patients with colostomies, Curry and Bargen (1935) found a similar disappearance of glucose after the solution had been allowed to remain in the lower colon for 3 hours. Further evidence that the

recovery of unabsorbed material is a reasonably accurate procedure is found in the work of Voit and Bauer (1869). In the course of their studies on the absorption of nutrient enemata, muscle albumen was given per rectum; some hours later, a cleansing enema led to the recovery of all the injected albumen except for 29 g. and an amount of nitrogen equivalent to this appeared in the urine as urea.

It is probable that some degree of fermentation does take place since several of the normal flora of the colon ferment glucose. I have found that when glucose solutions were incubated with suspensions of faeces at 37°C. for 2 hours, the loss of glucose was never more than 10 per cent; in one experiment, it was found that the loss in 24 hours was only 20 per cent.

70 to 80 per cent. of the enema glucose vanished yet fermentation of glucose and incomplete recovery of unabsorbed material due to inefficiency of the washout, cannot account for all the glucose lost. It follows, therefore, that some significance must be attached to the results obtained by this method. In other words, the glucose must have been absorbed.

The Effect of the Glucose Enema on Nitrogen Metabolism.

In view of the inconclusive results obtained from blood-sugar studies and from estimation of the residual glucose in the rectal washout the problem of glucose absorption from the rectum

was approached indirectly by determining what effect the enema had on nitrogen metabolism.

It is well known that if a subject on a low carbohydrate diet is given additional carbohydrate there is a reduction in the amount of nitrogen excreted, the carbohydrate having a sparing effect on nitrogen metabolism. If there is absorption from the rectum, glucose given by that route should have this effect in the same way as it has when given by mouth. This was tried in 10 subjects. They were given a diet of a calorific value sufficient for basal and energy requirements but in which the carbohydrate portion was limited to a quantity low enough to give a mild ketogenic diet. The protein, carbohydrate and fat contents were calculated from Rose's Dietetic Tables (1912). The daily output of nitrogen was estimated from 24 hours specimens of urine which had been preserved under toluol after collection. The total acidity and ammonia were also determined. When the nitrogen excretion had become constant on 3 successive days glucose enemata were given and the above urinary constituents estimated for a further period of at least 5 days. In Cases 1 and 2, the glucose enema was given once but as the effect was indefinite the routine was altered somewhat and more than one enema was given over a period of two days in the later studies. Variation was also made in the strength of the glucose solutions.

Great difficulty was experienced with this part of the

investigation. The diets were, of necessity, unpleasant and the subjects were only too ready to refuse or break them. In some cases it seemed impossible to obtain a constant excretion of nitrogen. For one or other of the above reasons 4 of the 10 cases had to be abandoned.

All the other six cases showed diminution in nitrogen excretion after rectal glucose. Unfortunately, in three of the subjects it was impossible to attain a sufficient constancy in the nitrogen excretion to determine definitely whether the reduction in the nitrogen excretion was caused by the glucose and not accidental. In these cases, R.W., M.McI. and M.W., the nitrogen excretion although fairly constant in the pre-period, became irregular after the expected drop and failed to regain the level of the pre-period. But for an accident the next case (M.S.) might have demonstrated the influence of rectal glucose conclusively. Nitrogen excretion in the pre-period was constant. As anticipated, it fell after glucose was given rectally and then regained the level of the pre-period. Unfortunately, on the second day of the post-period, an unknown quantity of urine was lost and the amount of nitrogen determined in the urine for that day was diminished. This mishap has rendered the figures for this study also indefinite.

In two cases, however, the amounts of nitrogen excreted varied within narrow limits in each of the three periods.

(Cases 5 and 6). A reduction in the nitrogen excretion was observed following rectal glucose and in the post-period the amount of nitrogen excreted daily returned to the level of the pre-period. These two cases definitely demonstrate that nitrogen sparing has taken place. This phenomenon must be regarded as evidence of absorption of glucose from the rectum. Although affording evidence of absorption of glucose from the enema, unfortunately these studies give no indication of the quantity of glucose absorbed.

Since, under the conditions of these studies, a mild ketosis was present, it was thought that the absorption of glucose might also be reflected by a diminution in the acidity and in the ammonia output of the urine. With the exception of Case 6 (J.C.) where a definite fall did occur in the total acidity after the glucose enemata, no marked response was observed in the total acidity or in the amount of ammonia excreted in the urine that could be attributed to the action of the glucose.

As has been mentioned above, the nitrogen excretion in the first two cases (R.W., M.McI.) after being fairly constant in the pre-period, became irregular when the glucose enema was given. Both of these cases received a hypertonic glucose solution (15 per cent) per rectum. It was thought that possibly the hypertonic solution might have been a factor in producing the

upset. Most of the further investigations were conducted with an isotonic glucose solution (5 per cent.). Although definite evidence is lacking that the hypertonic solution was responsible for the disturbance, it is at least noteworthy that the two conclusive studies were achieved using isotonic solutions of glucose.

Summary:

1. The changes in the peripheral blood-sugar level were observed in 36 fasting 'normal' subjects and in one case of hyperthyroidism following the rectal injection of glucose solutions of various strengths. In one of the normal cases, there was a significant rise, in all others, a slight fall in the blood sugar content was observed. No rise in the blood-sugar content followed the injection of a glucose enema in one case of hyperthyroidism.
2. In 15 of the above cases, the rectum was washed out at the end of the test period and the returned fluid examined for glucose. The percentage of the instilled glucose recovered varied between 7.45 per cent. and 60 per cent. but in only two cases was more than 50 per cent. of the instilled glucose recovered.
3. In 6 subjects out of 10 on a restricted carbohydrate

diet, rectal glucose was shown to influence the nitrogen metabolism. In 4 cases this influence was indefinite. Following the instillation of rectal glucose in the two remaining cases, however, a definite nitrogen-sparing effect was demonstrated.

4. Glucose is absorbed from a simple solution in water introduced into the lower bowel. The amounts of glucose absorbed vary considerably and cannot be assessed. Concentrations of 5, 10, 13.5 and 15 per cent. were well borne. Definite signs of irritation followed the use of 20 per cent. solutions. It is not possible to say, from this investigation what is the optimum concentration.

T A B L E 1.

BLOOD SUGAR STUDIES: SERIES 1.

Each case received 200 c.c. of 5 per cent. glucose in water per rectum.

Case	Age	Wt.	Blood sugar in mg.per 100 c.c.blood.					Glucose recovered in Rectal Washout.	
	Yrs.	Kg.	Fasting	30 min.	60 min.	90 min.	120 min.	G	Per cent of amt. given.
1. A.K.	10	29	75.6	66.6	69.8	68.8	74.0	3.5	35
2. T.P.	9	30	87.7	76.9	76.3	74.0	77.5	2.5	25
3. D.H.	10	35	80.6	80.6	81.3	73.5	81.3		
4. P.M.	5	17	52.4	44.0	37.3	38.9	34.7		
5. W.R.	11	27	47.6	41.0	41.3	50.0	48.0		
6. T.M.	7	20	80.7	63.3	78.8	73.0	67.5		
7. W.R.	11	27	80.5	74.3	80.5	84.4	76.4		
8. E.M.	9	16	87.7	85.5	96.1	91.7	90.9		
9. R.P.	9	23	112.3	97.1	85.5	78.1	76.4		
10. J.C.	6		54.3	44.2	49.3	53.4	47.2		
Mean Values			75.9	68.4	65.6	68.6	67.4		

TABLE 2.

BLOOD SUGAR STUDIES: SERIES 2

Each case received 200 c.c. of 10 per cent. glucose in water per rectum.

Case	Age	Wt.	Blood sugar in mg.per 100 c.c. blood.					Glucose recovered in rectal washout	
		Kg.	Fasting	30 min.	60 min.	90 min.	120 min.	g.	Per cent. of Amt. given.
11. J.R.	10	28	76.9	62.5	71.4	71.4	66.6		
12. C.F.	5	18	56.5	50.0	58.8	58.1	59.8	1.49	7.45
13. H.M.	11	37	60.2	61.3	58.8	62.5	58.6	12.0	60.0
14. R.C.	7	18	60.6	52.6	55.5	54.0	52.6	1.6	8.0
15. M.C.	6	13.5	83.3	77.0	78.7	62.5	73.5	2.0	10.0
16. E.M.	6	20	77.5	74.0	79.3	83.3	78.7	6.0	33.3
17. J.R.	10	23	111.1	116.0	71.4	74.0	76.9	10.9	54.5
18. A.K.	10	29	69.9	72.5	62.5	52.6	64.3	2.0	10.0
19. J.M.	8	23	66.6	67.5	63.3	64.5	68.0	4.0	20.0
20. A.C.	9	22	66.6	68.8	58.8	62.5	58.8	10.0	50.0
Mean Values,			72.9	70.2	65.9	64.5	65.8		28.1

TABLE 3.

BLOOD SUGAR STUDIES: SERIES 3.

Each case received 200 c.c. of 13.5 per cent glucose in water per rectum.

Case.	Age	Wt.	Blood sugar in mg. per 100 c.c. blood.				
		Kg.	Fasting.	30 min.	60 min.	90 min.	120 min.
21. J.S.	8	23	82.6	95.3	83.3	83.3	79.7
22. R.W.	11	32	80.6	81.4	85.5	79.4	77.0
23. W.M.	9	23	59.3	60.3	68.5	66.6	60.9
24. W.W.	10	27	88.2	84.0	81.3	80.6	87.9
25. J.L.	9	22	90.9	90.2	82.6	69.9	86.9
26. J.T.	11	27	96.2	86.9	67.5	74.6	68.0
27. A.C.	11	-	74.0	74.6	62.5	64.1	72.5
28. E.J.	8	21	83.4	78.7	90.9	86.9	85.5
29. M.L.	8	22	95.5	80.0	90.9	86.9	85.5
30. J.G.	9	22	74.6	71.9	71.4	65.8	63.3
31. M.McL.	8	-	88.5	87.5	85.5	86.9	83.3
Mean Values,			82.9	80.9	79.0	76.4	77.3

TABLE 4.

BLOOD SUGAR STUDIES: SERIES 4.

Each case received 200 c.c. of 20 per cent. glucose in water per rectum.

Case.	Age	Wt.	Blood Sugar in mg. per 100 c.c. blood.					Glucose recovered in rectal washout.	
		Kg.	Fasting	30 min.	60 min.	90 min.	120 min.	G.	Per cent. of amt. given.
32. J.R.	10	28	87.7	80.0	90.9	84.0	83.3	6.25	15.6
33. R.C.	7	18	100.0	68.9	117.6	125.0	125.0	5.0	12.5
34. J.T.	11	34	88.7	74.6	71.9	71.4	70.4		
35. S.R.	9	26	78.7	72.9	66.6	62.5	66.6	8.1	20.3
36. J.L.	11	32	86.2	66.6	71.4	64.9	63.3	9.3	23.3
Mean Values,			86.9	74.6	83.7	81.6	81.7		17.8

TABLE 5.

M.M., Act. 11 yrs., Weight 25 kg.: Hyperthyroidism.

Blood Sugar content after 25 gm. of glucose by mouth and as a 20 per cent. solution per rectum.

	Blood Sugar in mg. per 100 c.c. blood.				
	Fasting	30 min.	60 min.	90 min.	120 min.
Oral,	68.0	145.0	124.9	98.0	74.0
Rectal,	60.9	62.5	66.1	66.2	64.8

T A B L E 6.

NITROGEN METABOLISM STUDIES.

Case 1. (R.W.) Age, 10 years. Weight, 24 Kg.

Diet: Protein, 53 g.
Carbohydrate, 43 g.
Fat, 108 g.

Calories, 1346
AK/K Ratio, 1/1.9

Glucose Enema: 30 g. glucose in 200 c.c. water.

Date	Total Urinary Nitrogen g.
14/15	9.76
15/16	11.8
16/17	10.8
17/18	11.07
18/19	7.27
19/20	9.21
20/21	4.28
21/22	10.67
22/23	6.88
23/24	8.88
24/25	7.00
25/26	10.80

Enema 6 a.m. 19th.

TABLE 7.

NITROGEN METABOLISM STUDIES

Case 2. (M.McI.) Age, 11 years. Weight, 38 Kg.

Diet: Protein, 60 g.
Carbohydrate, 30 g.
Fat, 95 g.

Calories, 1215
AK/K Ratio, 1/2.1

Glucose Enema: 30 g. glucose in 200 c.c. water.

Date.	Volume of urine c.c.	Total Acidity as c.c. N/10 Ac.	Ammonia c.c. N/10 alkali.	Total Urinary Nitrogen g.
19/20	460	260.0	324.0	10.4
20/21	570	320.0	360.0	12.5
21/22	660	310.0	442.0	13.1
22/23	530	354.0	372.0	11.76
23/24	530	400.0	420.0	11.2
24/25	380	154.0	250.0	6.2
25/26	680	374.0	620.0	14.6
26/27	440	201.0	320.0	7.7
27/28	380	168.0	246.0	6.77
28/29	570	304.0	466.0	11.6

Enema 6 a.m. 24th.

TABLE 8

NITROGEN METABOLISM STUDIES.

Case 3. (M.W.) Age, 12 years. Weight, 32 Kg.

Diet: Protein, 67 g.
Carbohydrate, 51 g.
Fat, 126 g.

Calories, 1719.
AK/K Ratio, 1/1.9.

Glucose Enema: 15 g. glucose in 300 c.c. water.

Date.	Volume of urine c.c.	Total Acidity as c.c. N/10 Ac.	Ammonia c.c. N/10 alkali.	Total Urinary Nitrogen g.
19/20	830	196.0	336.0	8.88
20/21	560	196.0	292.0	8.93
21/22	740	222.0	266.0	8.12
22/23	1430	300.0	465.0	10.29
23/24	720	204.0	220.0	5.74
24/25	470	194.0	272.0	7.69
25/26	860	240.0	338.0	8.00
26/27	570	194.0	242.0	7.45
27/28	640	-	-	9.18

Enema 10 a.m. 22nd.
6 p.m. 22nd.
10 a.m. 23rd.
6 p.m. 23rd.

TABLE 9.

NITROGEN METABOLISM STUDIES

Case 4. (M.S.) Age, 9 years. Weight, 28.8 Kg.

Diet: Protein, 52 g.
Carbohydrate, 30 g.
Fat, 79 g.

Calories, 1150
AK/K Ratio, 1/1.9

Glucose Enema: 30 g. glucose in 200 c.c. water.

Date	Volume of urine c.c.	Total Acidity c.c. N/10 Ac.	Ammonia c.c. N/10 alkali.	Total Urinary Nitrogen g.
21/22	390	234.0	412.0	6.67
22/23	380	226.0	322.0	6.49
23/24	430	216.0	286.0	6.00
24/25	390	262.0	302.0	6.49
25/26	410	236.0	296.0	7.02
26/27	400	180.0	216.0	4.91
27/28	340	170.0	224.0	4.84
28/29	460	282.0	300.0	7.57
29/30	240[x]	164.0	174.0	3.84
30/31	490	256.0	282.0	6.24
31/1	480	256.0	324.0	7.24

Enema 6 a.m. 26th.
6 a.m. 27th.

[x]Urine lost.

TABLE 10.

NITROGEN METABOLISM STUDIES.

Case 5. (J.M.) Age, 7 years. Weight, 23.4 Kg.

Diet: Protein, 55 g.
Carbohydrate, 45 g.
Fat, 85 g.

Calories, 1165
AK/K Ratio, 1/1.6

Glucose Enema: 15 g. glucose in 300 c.c. water.

Date	Volume of urine c.c.	Total Acidity c.c. N/10 Acid	Ammonia c.c. N/10 alkali.	Total Urinary Nitrogen g.
17/18	630	314.0	272.0	10.39
18/19	510	332.0	226.0	10.29
19/20	620	306.0	264.0	11.54
20/21	540	242.0	260.0	10.32
21/22	740	228.0	292.0	10.91
22/23	910	270.0	286.0	9.70
23/24	770	224.0	276.0	9.98
24/25	500	228.0	236.0	9.77
25/26	520	302.0	256.0	10.75
26/27	570	360.0	284.0	11.79
27/28	550	350.0	264.0	10.67

Enema 10 a.m. 21st.
6 p.m. 21st.
10 a.m. 22nd.
6 p.m. 22nd.

T A B L E 11.

NITROGEN METABOLISM STUDIES.

Case 6. (J.C.) Age, 10 years. Weight, 32.25 Kg.

Diet: Protein, 47 g.
Carbohydrate, 51 g.
Fat, 109 g.

Calories, 1373
AK/K Ratio, 1/1.8

Glucose Enema: 15 g. glucose in 300 c.c. water.

Date	Volume of urine c.c.	Total Acidity c.c. N/10 Acid.	Ammonia c.c. N/10 alkali	Total Urinary Nitrogen g.
25/26	660	364.0	315.0	12.40
26/27	690	332.0	338.0	12.43
27/28	690	342.0	308.0	12.75
28/1	725[x]	341.0	368.0	13.03
1/2	725[x]	341.0	368.0	13.03
2/3	1230	372.0	423.0	11.14
3/4	740	274.0	386.0	11.68
4/5	740	314.0	438.0	13.96
5/6	960	362.0	474.0	13.47
6/7	950	376.0	464.0	12.56

Enema 10 a.m. 1st.
6 p.m. 1st.
10 a.m. 2nd.
6 p.m. 2nd.

[x]Specimens of the 28/1 and 1/2 were pooled since 150 c.c. of the former specimen had been added in error to the following day's collection.

B. THE ABSORPTION OF SODIUM CHLORIDE.

One of the commonest procedures in post-operative surgical treatment is the administration of rectal saline, either by small repeated enemata or by continuous proctolysis. Since 1909, when Murphy described his method of continuous proctolysis this has been used more and more widely. It is most surprising to find how small a number of investigations has been made on the rectal absorption of sodium chloride.

In most modern textbooks of physiology the statement is made that salts are absorbed by the large bowel, yet, there appears to be little experimental evidence to support this claim. A search of the literature on the subject of absorption from nutrient enemata has revealed only four works dealing with the absorption of rectal saline. In 1869, Voit and Bauer found that sodium chloride was excreted quantitatively in the urine of a dog after the animal had been given a solution of sodium chloride by rectum. Nakazawa (1925) and McNealy and Willems (1929) also found evidence of absorption of sodium chloride from the colon in experimental animals. Gompertz (1910) confirmed these observations in the human subject. Perusse (1932) investigated the absorption of fluid after various solutions, among them normal saline, had been given per rectum. He did not, however, concern

himself with the fate of the solute.

In this research the problem was approached on the supposition that, where the subject was already receiving an adequate supply of sodium chloride, the absorption of further chloride would be demonstrated by an increase in the amount of chloride excreted in the urine.

Two children were put on a constant diet to which no salt had been added in the cooking. By this means a fairly constant salt intake was ensured. In order to provide an abundant maintenance supply of chloride, however, two grammes of sodium chloride were added to the diet each day. The daily output of urine was collected under toluol and its chloride content estimated.

After a control period, Case 1 (C.R.) received an additional 5 g. of sodium chloride by mouth daily for three days; two days were allowed after this without extra salt for the excretion of chloride to regain its original level and then, 600 c.c.normal saline (0.9 per cent. NaCl) were given per rectum daily for a further period of three days. During this period, the child was given a cleansing enema early each morning. 300 c.c. of the saline were instilled at 10 a.m. and at 6 p.m. Case 2 (J.L.) did not have any extra chloride by mouth but, after a

control period, received 600 c.c. normal saline per rectum on each of three days. The enemata were all well tolerated and none was rejected.

Details of the results are given in the accompanying tables. In Case 1 (C.R.) a nicely balanced excretion of chloride was obtained and during Periods 2 and 3 where extra chloride was given first by mouth and later by rectum, approximately the same quantity of chloride was excreted in the urine in each period. In Period 2 the daily average of chloride excreted was 3.43 g. more than the daily average of the control period and in Period 3 it was 3.71 g. in excess. Diuresis was not marked in this case.

In Case 2 (J.L.) it was found that there was considerable variation in the quantity of chloride excreted from day to day. Because of this, the prolonged control period of eleven days was deemed necessary. During the period in which rectal saline was given, the amount of chloride excreted daily rose above that excreted on the peak days of the control period and the average daily output was 13.16 g. whereas the average for the control period was 5.58 g. per day. Thus, during the period in which additional chloride was given per rectum more chloride was excreted than was given in the food and in the rectal infusion. A marked diuresis took place during this period (approximately 600 c.c. per day) and it is probable that the increase in the chloride excretion was, in some part, due to

this.

Thus, in both cases administration of rectal saline was followed by an increase in the chloride excreted in the urine. This may be regarded as proof that sodium chloride is absorbed from the rectum.

Summary:

Prolonged study of two cases on constant diet, with the successive addition of oral and rectal chloride in one case and of rectal chloride only in the other showed that sodium chloride is readily and apparently almost completely absorbed from the rectum.

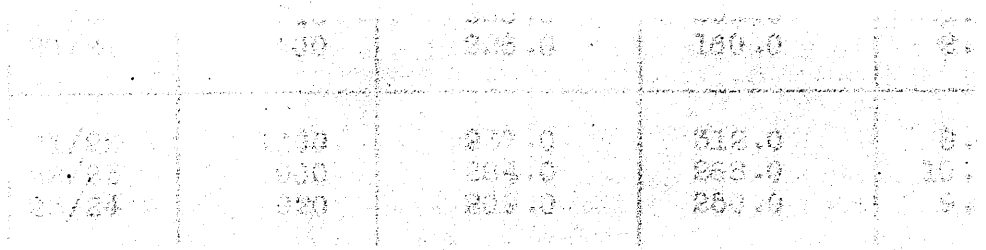


TABLE 12.

RECTAL ABSORPTION OF SODIUM CHLORIDE

Case 1. (C.R.) Age, 9 years. Weight, 25.7 Kg.

Diet: Protein, 60 g.
Carbohydrate, 146 g.
Fat, 63 g.

Sodium chloride, 2 g.

Enema: 300 c.c. normal saline (0.9 per cent. NaCl)

Date	Volume of urine c.c.	Total Acidity c.c. N/10 Acid.	Ammonia c.c. N/10 Alkali.	Sodium Chloride g.	
13/14	700	360.0	258.0	5.72	
14/15	1150	315.0	315.0	6.17	Period
15/16	520	212.0	178.0	5.65	1.
16/17	1040	258.0	291.0	9.97	
17/18	820	338.0	238.0	9.09	Period
18/19	960	336.0	266.0	8.18	2.
19/20	710	286.0	292.0	4.34	
20/21	400	226.0	160.0	2.58	
21/22	1160	237.0	312.0	8.36	
22/23	900	284.0	268.0	10.07	Period
23/24	920	209.0	250.0	9.76	3.

5 g. sodium chloride by mouth during Period 2.

300 c.c. normal saline per rectum at 10 a.m. and 6 p.m. daily during Period 3.

TABLE 13.

RECTAL ABSORPTION OF SODIUM CHLORIDE

Case 2. (J.L.) Age, 8 years. Weight, 22 Kg.

Diet: Protein, 60 g.
Carbohydrate, 146 g.
Fat, 63 g.

Sodium chloride, 2 g.

Enema: 300 c.c. normal saline (0.9 per cent. NaCl).

Date	Volume of urine c.c.	Total Acidity c.c. N/10 Acid.	Ammonia c.c. N/10 Alkali.	Sodium Chloride g.
4/5	1025	363.0	342.0	8.85
5/6	520	240.0	176.0	4.81
6/7	750	255.0	234.0	5.89
7/8	510	172.0	108.0	3.28
8/9	540	298.0	206.0	3.20
9/10	650	258.0	242.0	4.54
10/11	910	304.0	278.0	8.28
11/12	850	334.0	256.0	7.91
12/13	510	302.0	230.0	4.24
13/14	540	304.0	256.0	5.49
14/15	690	260.0	160.0	4.87
15/16	1130	396.0	315.0	12.43
16/17	1630	432.0	212.0	14.72
17/18	1190	345.0	264.0	12.40
18/19	940	422.0	158.0	8.75
19/20	1000	388.0	272.0	7.20
20/21	860	364.0	206.0	7.23

300 c.c. normal saline per rectum at 10 a.m. and 6 p.m. daily, on 15th., 16th. and 17th.

C. THE ABSORPTION OF PREDIGESTED PROTEIN.

In former times, protein was an important ingredient of the nutrient enema. Milk, eggs and bouillon were commonly used in its preparation. Sometimes wine was also included. The use of such enemata has continued into modern times. It is only in the latest edition (1940) of "Hutchison's Food and the Principles of Dietetics" that enemata containing protein other than that of predigested milk have been omitted.

When modern research took up the problem of absorption from the enema, the position of protein absorption was the first to be attacked. The investigations of Voit and Bauer, published in 1869, are considered the first in this field. Curiously enough, although nutrient enemata usually had protein-containing ingredients, interest in the absorption of nitrogenous substances from the rectum was not sustained and relatively few investigators have attempted to solve the problem in recent times. In fact, there have been only two papers published on the subject in the last 20 years.

Voit and Bauer made an extensive investigation of the rectal absorption of proteins and peptones. They found that, although egg albumen was not absorbed when given alone, it was apparently absorbed when given along with sodium chloride.

Muscle albumen and peptones were readily absorbed. The opinion of these workers was, however, that the procedure had no practical value. Ewald (1892) was convinced that a considerable amount of nourishment could be given in this way. He believed that predigested food was not necessary; in an earlier paper (1887), he described experiments where emulsified albumen was given per rectum to dogs and was apparently absorbed.

Boyd and Robertson (1906) gave mixed enemata of eggs, dextrose, milk and cod liver oil to a group of patients. The stools were examined for nitrogen, sugar and fat. Although there was considerable disappearance of sugar and fat, there was little difference in the amount of nitrogen given and that recovered in the stools. Boyd and Robertson concluded, therefore, that although considerable quantities of sugars and fats were absorbed, protein was poorly absorbed.

Langdon Brown (1911) found no increase in the nitrogen content of the urine after an enema of milk, dextrose, sodium bicarbonate and liquor pancreaticus. This mixture was incubated for only 20 minutes before its administration and may have been unsuitable for rectal absorption. Mutch and Ryffel (1913) found that a rectal washout yielded only 0.34 g. nitrogen after an enema of peptonised milk containing 2.8 g. nitrogen but, finding indican in the patient's urine, they concluded that considerable fermentation had taken place and that the nitrogen was not

necessarily absorbed. In a series of balance experiments, Bywaters and Short (1913) gave rectal injections of peptonised and of pancreatised milk. Trials were made with milk which had been pancreatised for 20 minutes and for 24 hours. No increase in the nitrogen excretion followed the taking of the peptonised milk. A small increase followed the injection of the milk pancreatised for 20 minutes and the maximum increase was found after milk treated for 24 hours was given. In the pre-period, of the experiment showing the maximum increase in the nitrogen excretion, the fasting patient was given glucose per rectum. This introduces a fallacy since, as I have shown, under such conditions one may expect a reduction in the nitrogen excretion from the protein-sparing action of glucose absorbed rectally. It is possible that, in this experiment of Bywaters and Short, the increase in the nitrogen excretion was a direct sequel to the withdrawal of glucose administration and not at all due to absorption of predigested milk.

In the course of an investigation on liver function, Gottschalk and Nonnenbruck (1923) compared the effects of giving a mixture of amino-acids ("Rectamin") by mouth and by rectum. They found that after oral ingestion there was a rise in the non-protein nitrogen of the blood but no increase in the amino-acid nitrogen of the urine. When the mixture was given rectally no rise in the non-protein nitrogen of the blood was observed

but the amino-acid content of the urine was increased. Nakazawa (1925) reported evidence of absorption of glycine from the large bowel in anaesthetised animals.

It appears that, although the older workers believed that native protein was well absorbed from the enema, later workers considered that absorption only took place from an enema of protein that had been predigested or from one containing amino-acids.

Children require protein for "wear and tear" and also for growth. They normally retain much more of the nitrogen taken in the food than do adults. Nevertheless, protein in excess of these requirements cannot be stored. It is metabolised and the end-products excreted in the urine. This investigation was planned on the hypothesis that, if the child were receiving sufficient protein for all his needs in his diet, additional nitrogenous material absorbed from an enema would be shown by an increased output of nitrogen in the urine. The protein chosen for use was casein and it was selected for a number of reasons. It has a high biological value, is easily handled and is available as an official preparation of the British Pharmacopoeia. Furthermore, in planning the study it was found that, under the present wartime restrictions, casein in the form of milk was a

protein which could be obtained with least difficulty to provide an abundant maintenance supply of protein in the diet. If rectal absorption were to take place, it seemed likely that the use of a protein, which was already being taken in great quantity by mouth, would demonstrate rectal absorption more readily by an increase in the nitrogen output in the urine.

Three children, two of nine and one of ten years of age, were put on constant high protein diets. These diets contained over 2 g. of protein per kilogramme of body weight and of this protein, about half was supplied in the form of milk and cheese. This quantity of protein was regarded as more than sufficient for the needs of the subject. Urine was collected in 24 hours specimens, preserved under tuluol and analysed for ammonia, urea and total nitrogen; in addition, in Case 3, the ammonia and amino-acid nitrogen were determined.

When nitrogen excretion had become constant three periods, each of three days, were studied. In the second period the patient received predigested protein per rectum. During each day of the second period a cleansing enema was given in the early morning, followed by a nutrient enema at 10 a.m. and again at 6 p.m.

The nutrient enema was prepared by digesting with trypsin powder a suspension of casein soluble in water. The amount of protein which had been split up by this laboratory

digestion was determined in each specimen. The enemata were all retained and did not produce any irritation.

Details of each study are given in the accompanying tables (Tables 15, 16 and 17).

In each case, the total nitrogen excreted rose during Period 2 by an amount approximately equal to the amount of non-protein nitrogen given per rectum; this point is demonstrated by the following table:

TABLE 14.

Case.	Urine: Total Nitrogen (g)			Total Non-Protein Nitrogen of Enemata (g)	Increase in Total Urinary Nitrogen Period 2 - Period 1. (g)
	Period 1.	Period 2.	Period 3.		
1. (J.R.)	23.20	28.59	26.22	5.94	5.39
2. (T.P.)	37.96	44.20	29.89[x]	6.60	6.24
3. (S.R.)	30.55	35.23	30.74	6.43	6.66

[x] Urine lost in this period.

In Case 3 (S.R.), in which the amino-acid nitrogen output was estimated, there was no marked increase after the enema in spite of the rise in total nitrogen. It would appear, therefore, that the non-protein nitrogen was absorbed and after absorption utilised in a manner similar to protein ingested by

mouth. This conclusion is further supported by an analysis of the figures obtained for the excretion of urea. In each of the three cases, there was a considerable rise in the amount of urea excreted during Period 2 (Table 18).

Under the conditions of this study, considerable quantities of nitrogenous material were absorbed from enemata. Gottschalk and Nonnenbruck claimed that a considerable amount of the absorbed material was taken up directly into the systemic circulation through the inferior haemorrhoidal veins, thereby avoiding the liver; this material was excreted by the kidneys as foreign matter. As in the present investigation no apparent increase in the excretion of amino-acid occurred in Case 3 and in each case there was an increase in the urea output in Period 2, it would seem that the digested protein introduced in the enemata was all absorbed into the portal system and deaminised by the liver.

An objection to giving protein per rectum was raised by Voit and Bauer. They argued that the amounts absorbed were so small that as a practical procedure such an enema was useless, since the absorption of a small amount of nitrogenous material stimulated the catabolism of more protein than it replaced. In this study, the amounts of nitrogen absorbed were equivalent to 12 - 13 g. of protein per day. The amounts given were chosen merely for convenience but after observing how well the

predigested casein enemata were tolerated, it seems likely that it is feasible to give sufficient quantities to be of practical value in nutrition.

Summary:

Three cases were studied before, during and after administration of predigested protein rectally. In all three there was a rise in total urinary nitrogen, practically equal to the amounts given by enema.

Non-protein nitrogen is absorbed quantitatively from an enema of predigested casein. It is apparently metabolised in a similar manner to nitrogenous food given by mouth.

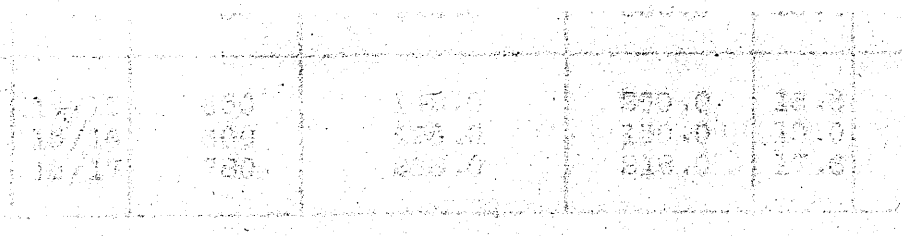


TABLE 15.

RECTAL ABSORPTION OF PREDIGESTED CASEIN

Case 1. (J.R.) Age 10 years. Weight, 23 Kg.

Diet: Protein, 65 g.
Carbohydrate, 92 g.
Fat, 94 g.

Enema: Casein Soluble (B.P.C.), 8.40 g.
Trypsin, ... 0.084 g.
Water, ... 250 c.c.

Total non-protein nitrogen of enemata, ... 5.94 g.

Period.	Date	Volume of urine c.c.	Total Acidity c.c. N/10 Acid.	Ammonia c.c. N/10 Alkali	Urea g.	Total Urinary Nitrogen g.
1.	8/9	510	184.0	342.0	13.8	7.30
	9/10	580	242.0	240.0	12.0	7.63
	10/11	620	172.0	238.0	15.8	8.27
2.	11/12	660	260.0	330.0	26.8	11.19
	12/13	840	114.0	302.0	18.3	8.64
	13/14	780	142.0	322.0	18.1	8.76
3.	14/15	650	142.0	260.0	16.6	8.61
	15/16	600	196.0	150.0	10.0	7.03
	16/17	780	268.0	218.0	17.6	10.58

During each day of Period 2 (11/12, 12/13 and 13/14) a nutrient enema was given at 10 a.m. and 6 p.m.

T A B L E 16.

RECTAL ABSORPTION OF PREDIGESTED CASEIN

Case 2. (T.P.) Age, 9 years. Weight, 29.6 Kg.

Diet: Protein, 103 g.
Carbohydrate, 127 g.
Fat, 104 g.

Enema: Casein Soluble (B.P.C.), 10 g.
Trypsin, ... 0.1 g.
Water, ... 300 c.c.

Total non-protein nitrogen of enemata, ... 6.6 g.

Period	Date	Volume of urine c.c.	Total Acidity c.c. N/10 Acid.	Ammonia c.c. N/10 Alkali	Urea g.	Total Urinary Nitrogen g.
1.	29/30	810	248.0	370.0	22.6	11.76
	30/1	710	348.0	340.0	26.6	12.20
	1/2	750	284.0	356.0	26.5	14.00
2.	2/3	880	362.0	356.0	30.0	15.4
	3/4	1300	375.0	432.0	36.3	17.6
	4/5	730	288.0	318.0	24.6	11.2
3.	5/6	930	320.0	436.0	31.6	14.78
	6/7	500	186.0	246.0	19.6	8.95
	7/8	560[x]	126.0	160.0	13.2	6.16

[x] Urine lost.

During each day of Period 2 (2/3, 3/4 and 4/5) a nutrient enema was given at 10 a.m. and 6 p.m.

TABLE 17.

RECTAL ABSORPTION OF PREDIGESTED CASEIN

Case 3. (S.R.) Age, 9 years. Weight, 26.28 Kg.

Diet: Protein, 88 g.
Carbohydrate, 172 g.
Fat, 93 g.

Enema: Casein Soluble (B.P.C.), 10 g.
Trypsin, ... 0.1 g.
Water, ... 300 c.c.

Total non-protein nitrogen of enemata, ... 6.43 g.

Period.	Date.	Volume of urine c.c.	Total Acidity c.c.N/10 Acid	Ammonia c.c.N/10 Alkali	Urea g.	Total Nitrogen g.	Amino-Acid N. mg.	Ammonia Nitrogen mg.
1.	15/16	630	194.0	234.0	19.6	9.63	25.1	254.8
	16/17	710	232.0	288.0	25.6	11.60	95.0	307.5
	17/18	620	238.0	255.0	19.3	9.32	73.7	267.5
2.	18/19	870	326.0	240.0	23.8	10.80	112.7	254.8
	19/20	1120	342.0	333.0	26.7	13.76	89.3	357.0
	20/21	830	238.0	318.0	21.0	10.67	38.5	364.0
3.	21/22	700	320.0	270.0	23.6	10.42	81.7	320.8
	22/23	710	276.0	308.0	23.5	11.89	112.0	238.0
	23/24	500	200.0	266.0	18.0	8.43	126.0	224.0

During each day of Period 2 (18/19, 19/20 and 20/21) a nutrient enema was given at 10 a.m. and at 6 p.m.

T A B L E 18.

RECTAL ABSORPTION OF PREDIGESTED CASEIN

Effect of Casein Enemata on the Excretion of Urea.

Period	Day	Urea Excreted (g.)					
		Case 1. (J.R.)		Case 2. (T.P.)		Case 3. (S.R.)	
		Per Day	Total for Period	Per Day	Total for Period	Per Day	Total for Period
1.	1	13.8)	41.6	22.6)	75.7	19.6)	64.5
	2	12.0)		26.6)		25.6)	
	3	15.8)		26.5)		19.3)	
2.	4	26.8)	65.2	30.0)	90.9	23.8)	71.5
	5	18.3)		36.3)		26.7)	
	6	18.1)		24.6)		21.0)	
3.	7	16.1)	43.7	31.6)	64.4	23.6)	65.1
	8	10.0)		19.6)		23.5)	
	9	17.6)		13.2)		18.0)	

D. ABSORPTION OF DRUGS FROM THE RECTUM

Since drugs have been administered by rectum for many years, apparently in certain cases with good effect, there are grounds for believing that absorption from the rectum does, in fact, take place. The variety of drugs given by rectum ranges from the very simple to the most complex substances and it is natural to doubt the capacity of the rectum to absorb all the substances offered to it. Of the drugs given rectally, clinical evidence of absorption is conclusive in a number of instances. Many drugs which are given per rectum produce no easily recognised effects and clinical demonstration of their absorption is difficult. Concerning the rates and completeness of absorption of rectally administered drugs relative to oral administration, few controlled studies have been made.

It was thought that whether a substance was or was not absorbed from the rectum might depend on the size of its molecule. With this hypothesis in mind it was decided to make trials with three drugs which varied considerably in their molecular structure. Potassium bromide, sodium salicylate and sulphanilamide were the drugs selected. Potassium bromide is an exceedingly simple salt which although foreign to the body is closely

related chemically to the chloride of the tissues. Sodium salicylate has a more complex molecule containing a benzene ring in its structure and the sulphanilamide molecule, in addition to a benzene ring also contains an amido sidechain. All three drugs have the merit that they are relatively easily estimated in the body fluids and in addition, in the case of salicylate and sulphanilamide where irritation of the gastric mucosa sometimes follows oral administration, rectal administration if proved at all efficient might be of considerable practical value.

1. RECTAL ABSORPTION OF POTASSIUM BROMIDE

It has been stated frequently that bromide is absorbed when administered rectally but I have been unable to find any experimental work substantiating this opinion. It is probable that simple bromide salts are well absorbed when given per rectum for the more complex substance, tribromethylalcohol ("Avertin") is definitely absorbed and now holds an established place in the realm of anaesthetics. Previous researches have shown that, in the human subject, two other halogen salts are well absorbed from the rectum. In an earlier section, I was able to confirm Gompertz' (1910) observation that chloride was well absorbed and Gompertz, Osborne (1922) and Cohn (1932) have shown that iodide is absorbed readily when given in solution per rectum.

A one per cent solution of potassium bromide in water was given per rectum to five children. One case received 1 g., each of the others 2 g., as a single dose. In each case the enema was completely retained. The drug was given during the forenoon. The urine was collected for several days and analysed for bromide. Details of each case are given in Table 19.

TABLE 19.

ABSORPTION OF POTASSIUM BROMIDE PER RECTUM

Case	Age (Yrs.)	KBr given in enema (1% soln.)	Urinary Bromide (as mg.KBr)			
			Before	1st.day	2nd.	Percentage excreted in 2 days
S.H.	9	100 c.c.(1 g.)	Nil	43.0	28.3	7.1
S.D.	5	200 c.c.(2 g.)	"	80.2	116.2	9.8
J.R.	8	200 c.c.(2 g.)	"	58.3	104.0	8.1
M.C.	6	200 c.c.(2 g.)	"	133.3	45.8	8.9
E.L.	4	200 c.c.(2 g.)	"	95.2	132.0	11.3

Although comparatively large quantities of bromide were given, no hypnotic or depressant effects were noticed in any of the children. Bromide, however, was found in the urine in each case though only a small fraction of the potassium bromide given was recovered during the period of the study. The quantities recovered varied little from case to case. In the 48 hours after the enema was given, the maximum amount recovered was 11.3 per cent of the quantity given and the minimum was 7.1 per cent. In the last two cases (M.C. and E.L.), the bromide excreted during the third day was determined. 44.6 mg. and 30.9 mg. were recovered respectively. In 1908, Hales and

Fishman gave single doses of sodium bromide by mouth to three students. The bromide excreted in the urine was estimated for several days thereafter. The results obtained by these workers are strikingly similar to these of the present investigation where the bromide was given per rectum. In one case, where one gramme of sodium bromide was given, Hales and Fishman found that 8.29 per cent appeared in the urine in 48 hours: in the other two, where two grammes of sodium bromide were given, 10.8 per cent was recovered from one in 48 hours whilst the other excreted 11.3 per cent in 56 hours.

The slow excretion of bromide was first shown by Bill (1869) to be due to the fact that, after absorption, it displaces some of the chloride of the body fluids. The bromide is only excreted when more chloride is absorbed.

Potassium bromide is absorbed from a rectal infusion. After single doses per rectum, it is excreted in the urine in amounts similar to those found after single doses given by mouth. It is therefore probable that the quantities absorbed are also similar whichever route is used for administration.

2. RECTAL ABSORPTION OF SODIUM SALICYLATE

The use of salicylates for the control of pain and temperature in acute rheumatic arthritis is well recognised. Since large doses have been employed toxic manifestations and gastric disturbances have been observed frequently.

In an attempt to minimise these undesirable effects Heyn (1912) gave sodium salicylate per rectum. He showed that the rectal instillation of 2 to 4 drachms of sodium salicylate in 6 ounces of starch water was followed by the relief of the joint pain and a fall in the temperature. Since these therapeutic effects were achieved by rectal salicylate Heyn considered the rectal route preferable to the oral one as thereby gastric disturbances were avoided. Irving (1923) reported similar experiences with rectal sodium salicylate in children; employing a dosage of 1 to 3 grains per pound of body weight, he noted that older children occasionally complained of headache and tinnitus within 15 to 45 minutes of the instillation of the sodium salicylate into the rectum. The early occurrence of these symptoms, if due to salicylism, suggest that salicylate is absorbed rapidly from the rectum. Recently Valesquez (1939) obtained satisfactory results with an isotonic solution of sodium salicylate (23.20 g. per litre) per rectum. Bullrich (1939) advocates an enema containing a mixture of the salicylates

of sodium, potassium and calcium. These workers reaffirm that, since gastric disturbances are thereby avoided, in the case of salicylate the rectal route is preferable to the oral one.

No controlled study has been reported on the rectal absorption of salicylate in the human subject. In 1933, Blume and Nohara compared the level of the salicylate in the blood and the quantity excreted in the urine of rabbits after oral and rectal administration. A slightly higher blood salicylate content was found after rectal administration than when the drug was given by mouth. 50 to 80 per cent of the salicylate was recovered in the urine whatever the method of administration. Blume and Nohara believed that absorption was more rapid when the salicylate solution was given by rectum than by mouth as the solution came immediately into contact with a large area of mucosa from which absorption could take place.

In the present inquiry one gramme of sodium salicylate and 2.5 grammes of sodium bicarbonate dissolved in 200 c.c. of water were given rectally in ten cases. Other ten children were given the solution in the same quantities by mouth. The total excretion of salicylate in the urine voided in the 36 hours following the administration of the salicylate solution, was estimated in each case. Varying periods are given for the

excretion of salicylate after oral administration. Hanzlik et al. (1917) gave 78 hours as a median for normal subjects. I found that most of the salicylate was excreted in 24 hours. With two exceptions, only a trace of salicylate was found in the urine excreted from 24 to 36 hours after oral administration. A similar period was found to be sufficient for the excretion of salicylate after rectal administration.

The results are given in Tables 20 and 21.

The quantities of salicylate recovered in the urine varied considerably in both series of cases. Where the solution was given by mouth, between 10.8 per cent and 64.9 per cent were recovered. On the other hand, when it was given per rectum, between 17 per cent and 52.5 per cent was recovered. The average recovery was approximately the same in each series, after oral administration 34.4 per cent and after rectal administration 33.4 per cent.

Most workers agree that salicylate is incompletely excreted, a part being destroyed in the tissues. The amount excreted appears to vary under different conditions; even under the same conditions there is some variation in the figures given by different workers. Where it was given over a period of several days, Hanzlik and Wetzel (1919) found that the total salicylate excreted in the urine varied between 75 per cent and 80 per cent. On the other hand, Morris and Graham (1931)

found that, over a period of six days, only 26.0 per cent to 37.6 per cent of the ingested salicylate was recovered in the urine but noted that, when sodium bicarbonate was given along with the salicylate, the urinary excretion rose to 80-91.4 per cent. Apparently the fraction of salicylate excreted in the urine is much smaller when small single doses are given than when such doses are given over a period of several days. Devrient (1921) recovered only from 1.01 to 14.68 per cent in the urine of patients who each had been given one gramme of sodium salicylate in a single dose.

A comparison of the results of the present investigation shows that there is no significant difference in the quantities of salicylate recovered in the urine after oral or rectal administration of sodium salicylate. There is apparently no notable difference in the degree of absorption when the drug is given in solution by either route. A comparison of the rate of excretion of salicylate given by mouth with the rate when given by rectum shows that excretion is more rapid when given by the mouth. The average amount excreted in 4 hours when the oral route was employed was 0.140 g. while by the rectal route 0.094 g. was excreted in the same time. This fact suggests that absorption may be slower when the drug is given per rectum. It is possible, however, that diuresis may also be a factor in determining the rate of excretion. In comparing the two series,

it was noticed that where a greater quantity of salicylate was excreted in the first four hours after the salicylate solution was given there was also a greater volume of urine excreted. It was also found that diuresis was greater when the drug was given by the mouth than it was after rectal administration.

Summary:

Sodium salicylate is readily absorbed from a rectal infusion.

The quantities of salicylate which are excreted after single doses of sodium salicylate, given either by mouth or by rectal infusion, are variable. The greater part of the absorbed salicylate is apparently destroyed in the tissues.

In children, excretion of salicylate is rapid after both oral and rectal administration but it is more rapid when given by the former route than by the latter.

As a therapeutic measure salicylate enemata could replace the oral administration of salicylate if necessary.

TABLE 20.

RECOVERY OF SALICYLATE FROM THE URINE AFTER ORAL ADMINISTRATION

Each case received the following solution by mouth.

Sodium salicylate		1 g.
Sodium bicarbonate		2.5 g.
Water	to	200 c.c.

Case	Age (Yrs.)	0-4 hours		4-24 hours		24-36 hours		Total recovered %
		Vol. c.c.	Na Sal. g.	Vol. c.c.	Na Sal. g.	Vol. c.c.	Na Sal. g.	
1. D.McQ.	9	350	0.286	700	0.363	210	Nil	64.9
2. M.McE.	8	250	0.106	400	0.156	300	F.t.	26.2
3. G.W.	5	400	0.034	300	0.208	900	Nil	24.2
4. J.R.	10	480	0.106	860	0.327	960	"	43.3
5. M.C.	6	300	0.131	500	0.040	550	"	17.1
6. R.C.	6	300	0.200	100	0.006	500	"	20.6
7. S.L.	12	225	Trace	260	0.200	80	"	20.0
8. H.P.	7	500	0.278	500	0.417	-	"	69.5
9. J.R.	10	70	0.064	240	0.044	500	F.t.	10.8
10. H.McD.	9	210	0.200	2200	0.275	-	Nil	47.5
Average		308.5	0.140	586	0.204			34.4

T A B L E 21.

RECOVERY OF SALICYLATE FROM THE URINE AFTER RECTAL ADMINISTRATION

In each case the following enema was given.

Sodium salicylate		1 g.
Sodium bicarbonate		2.5 g.
Water	to	200 c.c.

Case	Age (Yrs.)	0-4 hours		4-24 hours		24-36 hours		Total recovered %
		Vol. c.c.	Na Sal. g.	Vol. c.c.	Na Sal. g.	Vol. c.c.	Na Sal. g	
1. G.McL.	8	350	0.213	370	0.089	700	Nil	30
2. "	8	410	0.096	990	0.421	520	"	52
3. J.C.	7	65	0.028	320	0.267	800	0.080	38
4. A.C.	6	70	0.015	400	0.240	120	Nil	25.5
5. P.S.	5	80	0.027	200	0.159	110	F.t.	18.4
6. P.B.	9	325	0.030	700	0.495	250	"	52.5
7. M.H.	8	85	0.014	250	0.131	180	0.100	24.5
8. J.B.	10	410	0.156	480	0.385	320	Nil	54.1
9. H.S.	10	520	0.297	525	0.091	-	"	39.
10. A.M.	11	150	0.057	535	0.110	-	"	17
11. J.B.	5	-	-	-	0.274	-	F.t.	27.4
Average		247	0.094	475	0.240			33.4

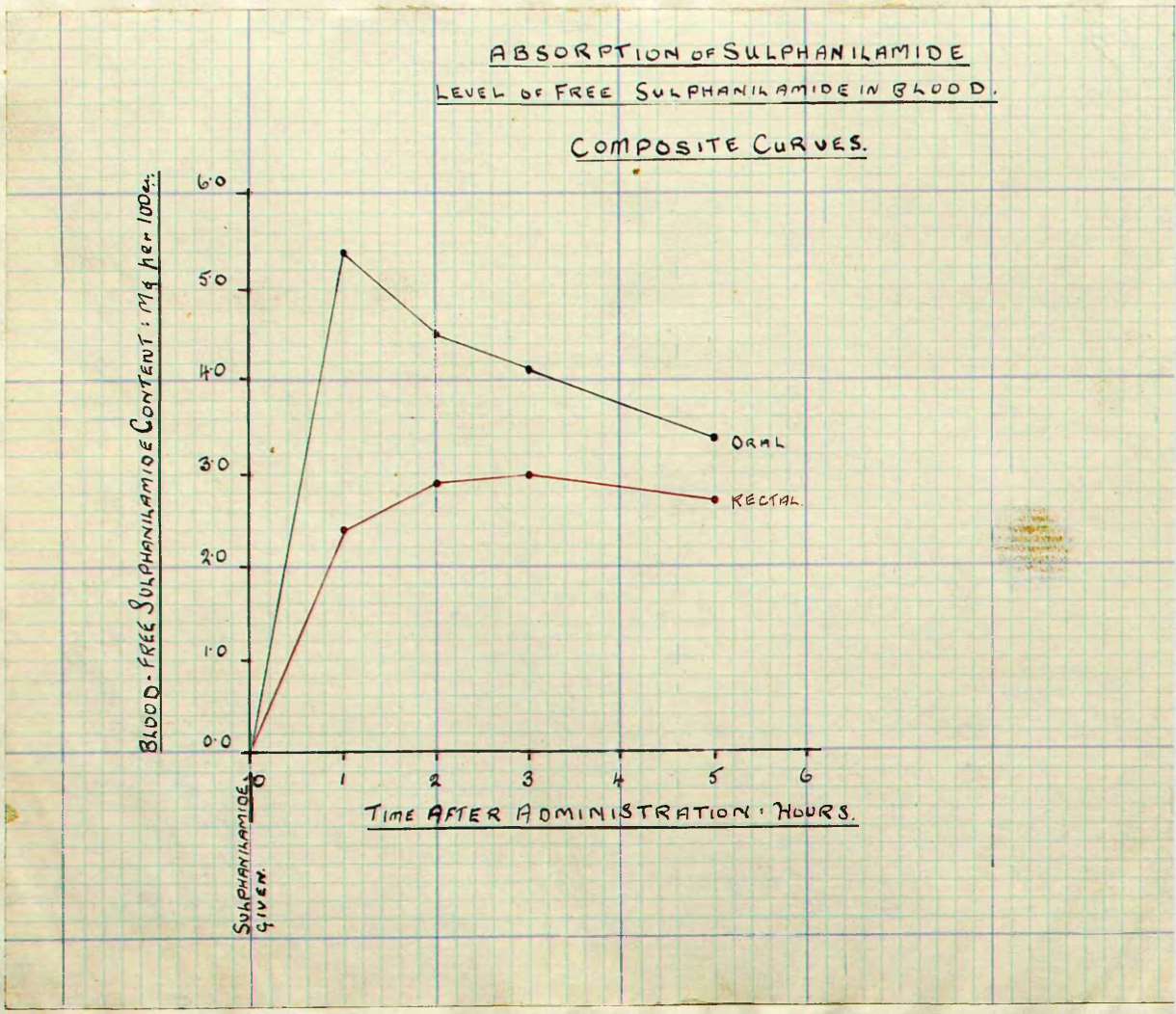
3. THE RECTAL ABSORPTION OF SULPHANILAMIDE

Since their introduction, the sulphanilamide group of drugs have been used extensively. It has been found that, following the high dosage necessary in treating certain conditions, patients often complain of nausea and vomiting is not infrequent. The employment of alternative methods of giving the drug may be necessary to maintain the requisite blood concentration. Under such conditions rectal administration, as a practical alternative to the painful and sometimes destructive intramuscular injection, suggests itself. That the rectal administration of sulphanilamide may be a procedure of practical importance is suggested by the work of Turrel, Marino and Nerb (1940). These workers obtained a concentration of from 9 to 15 mg. per cent total sulphanilamide in the blood after the rectal instillation of a one per cent solution of the drug over periods of 24 to 65 hours. When suppositories were used the maximum concentration obtained in the blood was 6 mg. per cent. Wood (1941) reported similar observations with a saturated solution of sulphanilamide. In one case he obtained a blood sulphanilamide concentration of 12.5 mg. per cent after 260 grains of sulphanilamide per rectum. This is a near approach to the maximum concentration obtainable in the blood but the dose could not be tolerated by more than a few individuals, if given orally.

The absorption of the drug when given by mouth and by the rectum has been compared. The concentration of free sulphanilamide in the blood and the excretion of total sulphanilamide in the urine has been estimated after giving the drug by mouth, in solution, and by the rectum, when in solution and in the form of suppositories.

One gramme of sulphanilamide dissolved in 200 c.c. of water was given by mouth to each of ten children. The free sulphanilamide content of specimens of capillary blood taken at one, two, three and five hours after the drug had been given, was determined. The total sulphanilamide was estimated in the urine collected for 36 hours. A second group of ten children received one gramme of sulphanilamide in 200 c.c. of water per rectum and a third group two suppositories, each containing 0.5 g. sulphanilamide: specimens of blood and urine were collected and the sulphanilamide content estimated in each case. No evidence of bowel irritation followed the administration of the solutions or suppositories in any of these cases. The results are shown in the following tables, (Tables 22, 23 and 24).

Where the sulphanilamide solution was given by mouth, the levels of free sulphanilamide in the blood after rising to a maximum at 1 hour, showed a progressive fall, though at 5 hours there were still considerable quantities of free sulphanilamide present in the blood. The recovery in the urine was incomplete.


ABSORPTION OF SULPHANILAMIDE
LEVEL OF FREE SULPHANILAMIDE IN BLOOD.
COMPOSITE CURVES.
BLOOD-FREE SULPHANILAMIDE CONTENT: MG PER 100 c.c.
6·0
5·0
4·0
3·0
2·0
1·0
0·0
ORAL
RECTAL
0
1
2
3
4
5
6
TIME AFTER ADMINISTRATION: HOURS.
SULPHANILAMIDE GIVEN.

The quantities recovered varied from 76.8 per cent to 25 per cent of the amount ingested, averaging 50.1 per cent.

Following rectal infusion of the sulphanilamide solution the free sulphanilamide content of the blood rose, in some cases to between 3 and 4 mg. per cent. The curve was, however, of a different shape; the peak being reached between 2 and 3 hours after the sulphanilamide was given. In all but one case there was still considerable free sulphanilamide present in the blood at the end of 5 hours. The free sulphanilamide content of the blood after the drug had been given in solution by mouth and by rectum is shown in the accompanying graphs. The average recovery of sulphanilamide in the urine, after the drug had been given in a rectal infusion, was 42.9 per cent.

Following the administration of the suppositories, in only two cases was there sufficient free sulphanilamide present in the blood in the ensuing 5 hours for an accurate quantitative estimation to be made. The average recovery in the urine (23.7 per cent) was much less in this than in the previous series.

From a study of the first group, it is evident that both absorption and excretion are rapid when sulphanilamide is given in solution by mouth. The average figure for recovery of total sulphanilamide is similar to that obtained by Scudi and Ratish (1938) in their three cases. In their investigation upon adults, 50 hours were found necessary for all the drug to be

excreted. In this study upon children, a period of 36 hours was found to be sufficient.

The figures obtained from estimations of sulphanilamide in the blood and in the urine after the rectal injection of a sulphanilamide solution indicate that it is readily absorbed from the enema. A comparison of the composite blood sulphanilamide curve with that obtained after the oral administration of the drug shows that absorption by the rectal route is definitely slower than when it is given by mouth. The fact that smaller quantities of sulphanilamide are recovered in the urine after rectal administration suggests that absorption may not be as complete as when it is given by mouth.

The failure to find more than traces of free sulphanilamide in the blood after the administration of suppositories shows that absorption is much slower when the drug is given rectally in a solid form. For absorption to take place solution is necessary. In the hind gut one of the principal functions is the absorption of water and, under normal conditions, the contents of the rectum are relatively dry. Thus, unless fluid is supplied, solution and absorption of a solidified preparation must be slow. That absorption of sulphanilamide from suppositories is less efficient is shown by the small amount recovered in the urine.

In treatment with this drug it is justly held that it

is of prime importance to attain a high concentration in the blood as soon as possible. The foregoing results suggest that, of the methods studied, oral administration achieves this object most effectively. In addition, estimation of urinary excretion suggests that absorption when the drug is given by the rectum is not as complete as when given by the mouth. In the main it appears that although oral administration is the method of choice, on occasion as in the presence of intractable vomiting, rectal administration of the drug in solution may be of value. In this case, large doses should be given. The use of suppositories appears to be of little value.

Summary: Sulphanilamide, when given in solution by mouth is absorbed with great rapidity. Apparently it is excreted more rapidly in children than in adults.

Sulphanilamide is readily absorbed from the rectum when given in solution. Absorption is, however, more slow and less complete than when the drug is given by mouth.

The drug is poorly absorbed from suppositories.

The administration of sulphanilamide in solution per rectum may be of considerable value. This procedure affords an additional channel of entry into the tissues for this valuable drug.

TABLE 22.

ABSORPTION OF SULPHANILAMIDE AFTER ORAL ADMINISTRATION

Each case received 1 g. sulphanilamide in 200 c.c. Water, by mouth.

Case	Age (Yrs.)	Blood: Free Sulphanilamide Mg. per 100 c.c.				Total Sulphanilamide in Urine	
		1 hr.	2 hrs.	3 hrs.	5 hrs.	Mg.	Percentage
1. G.W.	5	7.0	5.0	5.3	4.6	768	76.8
2. M.L.	7	-	4.7	4.4	3.7	744	74.4
3. J.L.	7	5.0	5.0	4.7	3.8	694	69.4
4. A.R.	9	5.3	4.0	3.0	2.8	500	50.0
5. J.L.	8	6.1	4.4	3.8	2.9	250	25.0
6. E.K.	5	5.7	5.0	4.4	3.6	323	32.3
7. J.D.	11	3.2	-	-	-	556	55.6
8. C.D.	8	5.0	4.0	3.2	2.0	315	31.5
9. M.M.	7	6.3	5.4	4.7	4.0	384	38.4
10. M.Q.	12	5.3	3.6	3.0	2.9	500	50.0
Mean Values		5.4	4.5	4.1	3.4	501	50.1

TABLE 23.

ABSORPTION OF SULPHANILAMIDE AFTER RECTAL ADMINISTRATION

Each case received 1 g. sulphanilamide in 200 c.c. water, per rectum.

Case	Age (Yrs.)	Blood: Free Sulphanilamide Mg. per 100 c.c.				Total Sulphanilamide in Urine	
		1 hr.	2 hrs.	3 hrs.	5 hrs.	Mg.	Percentage
1 G.W.	5	3.2	3.1	3.6	2.2	625	62.5
2 M.L.	7	2.1	2.9	3.9	3.1	591	59.1
3 J.L.	7	1.9	2.7	3.1	3.0	236	23.6
4 A.R.	9	2.5	3.0	2.7	2.5	515	51.5
5 J.L.	8	1.5	2.0	1.9	1.7	454	45.4
6 E.K.	5	2.0	2.8	2.2	f.t.	250	25.0
7 M.McE.	8	2.2	2.8	3.6	4.2	277	27.7
8 A.C.	6	2.8	3.9	3.6	2.9	500	50.0
9 A.B.	12	3.1	3.4	2.5	2.6	209	20.9
10 R.S.	8	2.5	2.7	2.9	2.3	528	52.8
Mean Values		2.4	2.9	3.0	2.7	429	42.9

T A B L E 24.

ABSORPTION OF SULPHANILAMIDE FROM RECTAL SUPPOSITORIES

Each case received 1 g. sulphanilamide in the form of two 0.5 g. rectal suppositories.

Case	Age (Yrs.)	Blood: Sulphanilamide Mg. per 100 c.c.				Total Sulphanilamide in Urine	
		1 hr.	2 hrs.	3 hrs.	5 hrs.	Mg.	Percentage
1. G.W.	5	f.t.	1.3	1.6	2.0	526	52.6
2. M.McC.	7	f.t.	f.t.	f.t.	f.t.	181	18.1
3. C.R.	9	Nil	f.t.	f.t.	f.t.	111	11.1
4. J.L.	8	f.t.	tr.	tr.	tr.	95	9.5
5. A.McD.	8	f.t.	tr.	tr.	-	238	23.8
6. M.H.	8	f.t.	tr.	tr.	tr.	357	35.7
7. M.C.	10	f.t.	f.t.	tr.	2.1	436	43.6
8. E.M.	10	f.t.	tr.	tr.	tr.	156	15.6
9. M.S.	9	f.t.	tr.	tr.	tr.	109	10.9
10. M.L.	7	f.t.	tr.	tr.	tr.	157	15.7
Mean Values						237	23.7

D I S C U S S I O N

The Range of Substances Absorbed: The modern attitude towards administration of substances by the lower bowel is that while the rectal route is good enough for simple solutions which have to be given when the patient is unable to take them by mouth - for example, the use of post-operative salines - it is unworthy of consideration when more complex substances have to be administered. That this ingenuous attitude was not always taken has been shown in the historical section of this thesis. I propose therefore to review the evidence in favour of the successful use of the lower bowel as a channel for supplying the body with various requirements.

In this investigation, it has been shown that predigested casein and sodium chloride are readily absorbed. Further evidence has been presented to support the view that glucose is absorbed from the rectum. The rectal absorption of potassium bromide, sodium salicylate and sulphanilamide has been demonstrated.

Rectal "Avertin" and rectal paraldehyde are both of established value. The former is given in a dosage calculated from the body weight, indicating that the anaesthetist expects a regular absorption to take place in every patient. The constancy of the results is an adequate testimonial to the ability

of the lower bowel to fulfil that expectation. The same remark applies to paraldehyde but for this drug there is no standard dosage based on the body weight. In the case of chloral hydrate, it has long been the practice of paediatricians when dealing with generalised convulsions to give by rectum twice the dose that would have been given orally.

Carpenter (1925) has shown that ethyl alcohol is readily absorbed per rectum and Sorensi (1935) maintains that in surgical practice enemata of wine are better than opiates in pre-operative and post-operative treatment.

Levy (1924) gave an aqueous extract of digitalis per rectum to a number of patients suffering from auricular fibrillation. He found that the same effect was produced in approximately the same period of time as when the drug was given by mouth. He believed the rectal route to be the one of choice for this drug as, in his opinion, the nausea and vomiting which often accompany the taking of digitalis are produced not by a central action in the medulla but by a local irritation of the gastric mucosa.

Curry and Bargen (1935), who had for their subjects, a number of patients with colostomies, were able to show that several substances were absorbed from the segment of large bowel between the colostomy opening and the anus. Atropine instilled into this segment of bowel produced dilatation of the pupil in

1½ to 3 hours; methylene blue and sucrose were recovered in the urine after being given in the same manner. Arsenic was recovered from the large bowel proximal to the colostomy opening several days after its instillation into the distal segment.

Some degree of clinical success has been reported following the use of an aqueous solution of neoarsphenamine per rectum. Fortunato (1923) found that of two cases treated in this way the Wasserman Reaction became negative in one and in the other it became much weaker.

Further evidence that more complex substances are absorbed when given rectally is afforded by the work of Peskind et al. (1924) and Resnikoff (1929). Peskind found that insulin given per rectum to rabbits was definitely absorbed but where human subjects were concerned variable results were obtained. Resnikoff found that a reticulocyte response followed the rectal administration of a cod liver extract to a patient suffering from hyperchromic anaemia.

From the foregoing, it can be seen that the range of substances absorbed is fairly comprehensive. Simple salts, phenols, alcohols, alkaloids, monosaccharides and disaccharides, amino-acids and even proteins are absorbed rectally. It would seem, however, that the size of the molecule does influence the absorption of substances given rectally, despite the fact that the large protein molecules can be absorbed. As the molecule

becomes more complex so does the rectal absorption tend to become more variable. The rectal absorption of simple substances such as sodium chloride, sodium salicylate and alcohol is apparently constant and the absorption of the amino-acids of predigested casein seems to be as complete by rectum as by mouth. On the other hand, the rectal absorption of albumen is uncertain. How complete is the absorption of glucose after the administration of a glucose enema is still obscure though the work here recorded suggests that up to 80 per cent of the instilled glucose may be absorbed.

Thus, it may be taken as proved that the rectum is able to absorb a great variety of substances. But the quantities absorbed become less certain and the rate of absorption is probably much slower when relatively complex substances are used.

The Path of Absorption: Many writers on the subject of rectal feeding and rectal medication have discussed the possible path of absorption of rectally administered material. Studies designed to elucidate this problem have produced interesting results.

Two theories were formulated. On the one hand, some held that absorption took place from the rectum and lower colon. On the other hand, it was surmised that, when the clyster was thrown into the body, it was borne through the large bowel to

the small intestine where it was absorbed. This assumes that propulsion in an upward direction is not an extraordinary occurrence.

The phenomenon of anti-peristalsis has been well recognised for many years. Sennest recorded the most remarkable case of this kind. Because she vomited numerous clysters, a girl who had "the iliac passion" was given suppositories which were tethered externally with threads. However, these were promptly vomited also, with pieces of thread still attached. In modern times, Parkes (1904) has collected a number of cases of faecal vomiting in hysterical patients. Other evidence also exists in favour of enemata reaching the small intestine. Cannon (1902) in an investigation of the movements of the gut, by means of X Rays, gave a nutrient enema which he had rendered opaque by mixing it with barium. The behaviour of the bowel was observed and it was found that the enema was all carried into the small bowel by anti-peristaltic waves. Hurst (1925) states that when an opaque enema is given at no greater pressure than eighteen inches of water, part of the enema passes through the ileo-caecal valve in a number of cases. From an analysis of a large number of cases, Barclay (1933) found that in 13 per cent some of the opaque enema passed into the small intestine.

A number of workers have paid particular attention to the large bowel as the probable site of absorption. In some

cases it has been possible to study absorption in the human subject from segments of large bowel which had been isolated from the rest of the alimentary canal. In a series of cases Curry and Bargen (1935) found definite evidence of absorption from a distal segment of bowel, comprising the sigmoid colon and rectum, which was separated from the proximal bowel by a colostomy. In their studies on the rectal absorption of sulphanilamide, Turrel, Marino and Nerb (1940) found, in one case where the rectum had been isolated and formed a blind pouch, that sulphanilamide was readily absorbed from the actual rectum when a solution of the drug was instilled into it.

Levy gave an aqueous extract of digitalis to a number of patients and found that it was absorbed. The volumes of the solutions were from 8 c.c. to 20 c.c. washed in with 25 c.c. of water. To determine to what depth the solution penetrated, he gave similar small quantities of 15 per cent sodium iodide solution and watched the shadow with X Rays. In all cases the shadow was confined to the sigmoid colon and rectum; it disappeared in from 4 to 6 hours.

Thus, it can be seen that absorption can take place from all parts of the large bowel. However, where a large enema is given the whole colon is filled and in a proportion of cases, some of the enema reaches the small intestine. Consequently, absorption may take place from a large area of colonic mucosa

and in some cases, the substance of the enema reaches the highly absorptive mucosa of the ileum.

Gottschalk and Nonnenbruck, Rubino and Varela and Levy were of the opinion that absorption of rectally administered substances followed a different route from that taken by food given by mouth. They believed that amino-acids and glucose absorbed from enemata did not enter the portal system and were excreted in the urine as foreign material. Further work has failed to substantiate this theory. In the present work it was found that after enemata of predigested protein the amino-acid content of the urine was unaltered but the urea content rose markedly. Thus, the absorbed amino-acids must have been deaminised. This is only possible in the liver and to reach it, the amino-acids had to enter the portal circulation. There can be little doubt that the path of absorption from the extreme caudal end of the bowel is probably through the inferior haemorrhoidal vein into the systemic circulation but except in the case of very small infusions or of suppositories, this route cannot be of great importance. In fact, the term "rectal absorption" is a misnomer.

The agglomeration of evidence favours the conclusion that, whilst solutions administered per rectum may reach the small intestine, the achievement of this objective is not of paramount importance as absorption can take place in any part of the lower bowel. Thus, high delivery of nutrient enemata is

unnecessary. In the extensive search of the literature undertaken in this study, I have failed to find any scientific basis for the belief that raising the foot of the bed after a nutrient enema is given directly helps absorption by assisting the passage of the nutrient fluid towards the upper bowel. This is borne out by the present work where no steps were taken to promote absorption by elevating the foot of the bed or raising the child's pubis on pillows. Nevertheless, raising the foot of the bed may help the patient to retain enemata. Hurst (1919) has shown that a rise in the intra-rectal pressure initiates the act of defaecation. By raising the patient's pubis this may be avoided.

The Quantity Given: Many objections to the use of nutrient enemata have been made on the grounds that no appreciable quantity of food could be given per rectum. In fact, Pasteur (1904) asserted that the only value of nutrient enemata was in the fluid that they supplied. He claimed that he obtained as good effects with tap water as with nutrient enemata. Boyd and Robertson (1906), using mixed enemata of eggs, dextrose, milk and cod liver oil, considered that sufficient calories could not be supplied by this means. They found that most of their patients lost considerable weight during the fast period. Gros (1898) believed that in the majority of cases, it was possible to maintain the initial weight during a period of exclusive rectal feeding.

However, examination of his protocols shows that losses of 4 to 5 Kg. occurred in fast periods of 12 to 17 days in a number of his cases. More recently Pressman (1930) calculated that, even if all the glucose given rectally were absorbed, not more than 600 calories could be supplied by use of glucose solutions in small repeated enemata or in continuous proctolysis. On the other hand, a case reported by McLendon, Cavett and Johnson (1937) suggests that rectal feeding may supply a considerable proportion of the body's needs. In this case, an ileo-caecostomy had previously been performed and it was known that fluid could pass through the stoma from caecum to small intestine. This factor may have influenced the results since it is possible that much of the nutrient fluid reached the ileum. The enema consisted of a mixture of amino-acids, glucose and alcohol. Most of the energy requirements of the patient were supplied by the alcohol. Rectal feeding was continued for 2 months and during this time the loss in weight was only about one pound per week.

It is interesting to compare the losses in weight occurring in patients on exclusive rectal feeding with that resulting from an absolute fast. In his investigation on metabolism during starvation, Cathcart (1907) found that Victor Beauté lost 7.8 Kg. in fasting for 15 days. This loss is

considerably greater than that reported by those investigating the nutrient enema where exclusive rectal feeding has been used for a like period. Thus, it seems that although rectal feeding is not wholly sufficient for maintenance, nevertheless sufficient nourishment can be given by this route to make the procedure of value. It was not feasible to investigate this aspect of rectal feeding since suitable cases are rare in children. It is possible that if enemata suitable in composition and adequate in quantity were used, results as favourable as those obtained in the case reported by McLendon, Cavett and Johnson would be obtained. In all the other investigations with exclusive rectal feeding, the enemata were not predigested and most of them were inadequate in amount.

It is widely held that if enemata are to be retained, only a very small quantity can be administered at one time. There does not seem to be any sound basis for this belief. Murphy (1909) devised a method for continuous proctolysis with which he claimed that the average quantity of fluid retained by an adult was 18 pints in 24 hours. The salient features of this procedure are as follows. A wide tube with no constrictions in its length should be used. The base of the fluid container should not be more than 6 inches above the level of the patient's buttocks and the temperature of the fluid entering the rectum, 100^{o}F. Such great quantities of fluid are seldom given these

days but Murphy's method, because it requires frequent attention, has fallen into disuse. The volumes commonly recommended for an adult are from 4 to 6 fluid ounces. I found that where a non-irritant enema was used, 200 to 300 c.c. (approximately 7 to 10 fl.oz.) could be retained with ease by children between the ages of 5 and 13 years.

In giving retention enemata, the important factors appear to be the following. A bland fluid should be used at a temperature of 100°F: it should be administered slowly, about 10 c.c. per minute, in this way preventing a sudden increase in the intra-rectal pressure. It was found in this study that to obtain this rate of flow, the fluid container required to be held not more than 18 inches above the level of the bed.

General Conclusion.

In view of the historical evidence and of the actual confirmatory figures obtained in the course of this study it must be obvious that the lower bowel merits much more consideration from the clinician and pharmacologist than has been acceded it in recent times. It is only in the presence of diarrhoea or of an obstructive lesion of the bowel that the rectal route would cease to be available. Its use requires no complicated apparatus nor high degree of skill. The solutions to be used do not need to be prepared with the meticulous accuracy so essential for intravenous or subcutaneous administration. One allowance, however, must be made. Rectal administration requires more time and a higher dosage than would be necessary if the substances were given by mouth. It is suggested, therefore, that modern medicine is ignoring an important channel of supply which could be of great value, complementary to the oral route as a rule but in a crisis capable of replacing it entirely. It is fortunate that this has been found to be true for young children. The sick child no less than the sick adult dreads the sight of the needle for the introduction of subcutaneous or intravenous solutions. Further, difficulty in establishing intravenous delivery is often experienced with children.

Proctolysis possesses another advantage in that it

is the only extra-buccal channel through which nitrogenous food can be given.

A more general appreciation of the possibilities of rectal administration of fluid, nutrient solutions and of a large variety of drugs would certainly lead to the widespread use of this route and to the alleviation of the patient's condition without resorting to the more unpleasant and troublesome substitutes for oral treatment.

General Summary.

The history of rectal alimentation has been outlined.

The nutrient enema has been discussed and an investigation into the rectal absorption of glucose, sodium chloride and predigested protein described. It has been shown that glucose is definitely absorbed although it was not possible to determine how completely it is absorbed. Sodium chloride is apparently almost completely absorbed from the rectum. Predigested protein is also readily absorbed, apparently completely.

The rectal absorption of potassium bromide, sodium salicylate and sulphanilamide has been studied and it has been shown that, in the case of sodium salicylate and sulphanilamide, rectal administration could be a practical proposition.

An attempt has been made, by a discussion of rectal alimentation in general, to estimate the present value of the rectal channel in the administration of food and drugs.

APPENDIX 1.

SOLUTIONS USED FOR RECTAL INFUSION

(a) The glucose solutions were prepared from pure dextrose (B.P.) and distilled water. They were boiled before use.

(b) The sodium chloride solutions used were the ordinary sterile "normal" saline (0.9 per cent NaCl) prepared for general use in the hospital.

(c) The predigested casein solution was prepared in the following manner. A quantity of casein soluble (B.P.C.) was mixed with a hundredth of its weight of trypsin powder and triturated with distilled water. This mixture was placed in the incubator overnight (about 18 hours) and the next day boiled before use. The pH of this mixture, after incubation, was found to be between 7 and 7.5. In order to determine the amount of protein that had been converted into amino-acid, a sample was treated with 15 per cent trichloracetic acid to precipitate the undigested fraction and the total nitrogen of the filtrate determined.

(d) The potassium bromide solutions were simple solutions of the drug in water. They were boiled before use.

(e) The salicylate solutions were prepared by dissolving the requisite quantities of sodium salicylate and sodium bicarbonate in boiled distilled water.

(f) The sulphanilamide solutions were prepared by dissolving the pure drug (para-amino-benzene sulphonamide) in distilled water. The solutions were sterilised by boiling before use.

The sulphanilamide suppositories were those prepared by the British Drug Houses (Suppository Sulphonamide-P).

APPENDIX 2.

BIOCHEMICAL METHODS

(a) The Blood Sugar Content: Specimens of capillary blood were obtained from ear or finger and received into small glass tubes containing about 4 mg. of a mixture of sodium fluoride and potassium oxalate in the ratio of 3/1, the fluoride-oxalate mixture acting as anticoagulant and preservative. Estimations of the blood sugar content of these specimens were carried out within an hour or two. The method of Folin and Wu as modified by Herbert and Bourne (1931) was used.

(b) Glucose in the Rectal Washout: The returned fluid was made up to a definite volume with distilled water and mixed. It was then filtered through glass wool to remove gross particles. The glucose content of the filtrate was estimated by Benedict's (1911) method for sugar in the urine. The copper solution was standardised against a solution of pure glucose before use.

(c) The Chloride Content of the Urine: Van Slyke's (1924) method was used for this estimation. To a specimen of urine, a silver nitrate solution was added in excess to precipitate all the chloride. Concentrated nitric acid was then added and the mixture allowed to digest on the hot place. After cooling, the excess silver nitrate was titrated against a potassium thiocyanate

solution.

(d) The Total Nitrogen of the Urine: This was determined by the macro-Kjeldahl method. Each estimation was done in duplicate.

(e) The Ammonia Content of the Urine: Urinary ammonia was estimated by the formalin titration method.

(f) The Urea Content of the Urine: The Hypobromite method was used for this estimation.

(g) The Ammonia Nitrogen of the Urine: For this estimation, the aeration method of Folin was used. A specimen of urine was transferred to an aeration tube and rendered alkaline with sodium carbonate. A current of air was passed through the solution and the liberated ammonia absorbed by a measured volume of a standard sulphuric acid solution. The excess sulphuric acid was titrated against a standard solution of sodium hydroxide.

(h) The Urinary Amino-Acid Content: The formol titration method of Hénriques and Sørensen (1909) was used. The urine was treated with barium chloride and barium hydroxide to precipitate phosphates and then filtered. The filtrate was made definitely acid to litmus and then neutralised with sodium hydroxide, using phenol phthalein as indicator. Neutral formol was added and the mixture titrated against a standard sodium hydroxide solution. This titration gave the amino-acid nitrogen plus the ammonia nitrogen. The amino-acid nitrogen was obtained by subtracting

the ammonia nitrogen figure estimated by Folin's method.

(i) The Bromide Content of the Urine: Bromide was determined by the method of Behr, Palmer and Clarke (1930). The specimen of urine was freed from all organic matter by ashing in a muffle furnace at a temperature of between 460° and 475° Centigrade for several hours after treating with concentrated potassium hydroxide. In an alkaline medium, bromide is stable at this temperature. After extracting, filtering and evaporating the filtrate, it was returned to the furnace for a further half hour at the same temperature. The residue of this second ashing process was extracted with water, filtered and the filtrate made up to a definite volume. A portion of the filtrate was transferred to a separation funnel where it was treated with a solution of potassium permanganate in phosphoric acid. The bromine liberated by this reaction was extracted with carbon tetrachloride. To remove traces of chlorine, this extract was reduced by sodium sulphite, reoxidised and the liberated bromine extracted with carbon tetrachloride. After performing this operation once more, the final extract was run into a potassium iodide solution and the liberated iodine titrated against a standard sodium thiosulphate solution.

(k) The Salicylate Content of the Urine: The steam distillation method of Thoburn and Hanzlik (1915) was used. A specimen of urine was treated with syrupy phosphoric acid and

boiled gently to break up the conjugated form (salicyluric acid) in which salicylate is excreted in the urine. The flask containing this mixture was then connected to the distillation apparatus and the salicylate distilled over into a measuring cylinder. The distillation was accomplished by keeping the contents of the distilling flask boiling gently and at the same time bubbling steam through the flask from a second one which was connected to it. The distillate was made up to a definite volume. To an aliquot portion of the distillate, iron alum was added and a pink colour produced. This solution was then compared with a standard solution of sodium salicylate similarly treated with iron alum.

(1) The Sulphanilamide Content of the Blood and the Urine: Sulphanilamide determinations were made by the method of Bratton and Marshall (1939). Specimens of capillary blood were obtained from ear or finger and received into small glass tubes containing a few milligrammes of potassium oxalate. A measure quantity of this specimen was laked with a saponin solution and the proteins precipitated with trichloracetic acid. To the protein-free filtrate, solutions of sodium nitrite, ammonium sulphamate and N-(1-naphthyl) ethylenediamine dihydrochloride were successively added. The intensity of the pink colour, so produced, was then compared with that of a standard solution of sulphanilamide similarly treated. In the determination of total sulphanilamide

in the urine, it was first necessary to hydrolyse the acetyl fraction. A specimen of urine was diluted with water, 1 in 25 or 1 in 50. Five cubic centimetres of hydrochloric acid (4 N.) were added to 50 c.c. of the diluted urine and the volume made up to 100 c.c. A portion of this second dilution was then heated in a boiling water bath for one hour. After cooling and adjusting the volume to make up for loss due to evaporation, the solution was treated as from the filtrate stage of the estimation in the blood.

APPENDIX 3.

B I B L I O G R A P H Y

Auchinachie, D.W., McLeod, J.J.R. and Magee, H.E., (1930), J.Physiol., 69: 185.

Barclay, A.E., (1933), "The Digestive Tract", London, 151.

Bartholin: quoted by Gros.

Bauer, J. and Monguio, J., (1932), Klin. Wochenschr., 11: 1820.

Behr, L.D., Palmer, J.W. and Clarke, H.T., (1930). J.Biol.Chem., 88: 131.

Benedict, S.R., (1911), J.Amer.Med.Assoc., 57: 1193.

Bergmark, G., (1915), Skand.Arch.f.Physiol., 32: 355.

Bill, J.H., (1869), Amer.J.Med.Sc., 56: 17.

Black, W., (1732), "An Historical Sketch of Medicine and Surgery", London, 14.

Blume, W. and Nohara, F.S. (1933). Arch.f.exp.Path.u.Pharm., 173: 413.

Boyd, F.D. and Robertson, J., (1906), Scottish Med. and Surg.J., 18: 193.

Bratton, A.C. and Marshall, E.K., Jr., (1939). J.Biol.Chem., 128: 537.

Bryan, C.P., (1930), "The Ebers Papyrus", London: 57.

Bullrich, R.A., (1939), Prenza med.argent., 26: 1277.

Burget, G.E., Moore, P.H. and Lloyd, R.W., (1933), Am.J.Physiol., 105: 187.

Cannon, W.B., (1902), Am.J.Physiol.: 6: 251.

Carpenter, T.M., (1925), "Human Metabolism with Enemata of Alcohol, Dextrose and Levulose", Carnegie Institue of Washington, Publication, No.369.

Cathcart, E.P., (1907), J.Physiol.: 35: 500.

Cholmley, H.P., (1912), "John of Gaddesden and the Rosae Medicinae". London.

Cohn, B.W.E., (1932), Arch.Int.Med.: 49: 950.

Collens, W.S. and Boas, L.C., (1933), Arch. Int. Med.: 52: 317.

Corkill, A.B., (1936), M.J.Australia: 1: 807.

Curry, F.S. and Bargen, J.A., (1935), Surg.Gynaec. and Obstet.: 60: 667.

Davidson, J.N. and Garry, R.C., (1939), J.Physiol.: 96: 172.

De Graaf, Regnier, (1668), Thesis, "De Clysteribus", quoted by Friedenwald, J. and Morrison, S., (1940), Bull.Hist.Med.: 8: 68 and 239, also by Gros.

Devrient, D., (1921), Arch.f.exp.Path.u.Pharm.: 90: 242.

Ebeling, W.W., (1933), Arch.Surg.: 26: 134.

Ewald, C.A., (1887), Zeitschr.f.Klin.Med.: 12: 407.

Ewald, C.A., (1892). "Lectures on Diseases of the Stomach". London, 2: 313.

Fantus, B., (1936), J.Amer.Med.Assoc.: 107: 14.

Fleming, G.B., (1919), J.Physiol.: 53: 236.

Fortunato, F., (1923), Arch.Paed.: 40: 836.

Franke, W. and Wagner, R.J., (1924), J.Met.Research: 6: 375.

Gale, T., (1586), "The Whole Worke of that famous chirurgion Master John Vigo". London. 341.

Galen, "De Causis Symptomi", 1: iii, quoted by Ewald (1887).

Garrison, F.H., (1929), "History of Medicine". Philadelphia, 158.

Gompertz, L.M., (1910), Yale Med.J.: 17: 240, quoted by Carpenter.

Gottschalk, A. and Nonnenbruck, W., (1923), Arch.f.exp.Path.u.Pharm.: 99: 300.

Gros, A.P., (1898), Thesis. "Traitement de certaines maladies de l'estomac par la cure de repos absolu et prolongé de l'estomac avec alimentation rectale exclusive". Paris.

Hales, W. and Fishman, C., (1908), Am.J.Physiol.: 22: 32.

Hanzlik, P.J. and Scott, R.W. and Thoburn, T.W., (1917), J.Pharm.Exp.Therap.: 9: 247.

Hanzlik, P.J., Wetzel, N.C., (1919), J.Pharm.Exp.Therap.: 14: 25.

Hari, P. and von Halasz, A., (1918), Biochem.Ztschr.: 88: 337

Henriques, V. and Sørensen, S.P.L., (1909), Z. Physiol. Chem.: 64: 120.

Herbert, F.K. and Bourne, M.C., (1931), Brit.Med.J.: 1: 94.

Heyn, L.G., (1912), J.Amer.Med.Assoc.: 58: 1013.

Hubbard, R.S. and Wilson, D.C., (1922),
Proc.Soc.Exper.Biol. & Med.: 19: 292.

Hurst, A.F., (1919), "Constipation and Allied Intestinal Disorders". London.

Hurst, A.F., (1925), Brit.Med.J.: 145.

Hutchison, R. and Mottram, V.H., (1936),
"Food and the Principles of Dietetics". 8th.Edition, London. 600.

Irving, G.R., (1923), Arch.Paed.: 40: 832.

Julesz, M. and Winkler, E., (1932),
Zschr.f.ges.exper.med.: 80: 823.

Langdon Brown, W., (1911), Proc.Royal Soc.Med., Therap.S. 43: 63.

Latham, R.G., (1848), "The Works of Thomas Sydenham". London.

Lee, A. (1831), "Celsus de Medicina". London. 1: 108.

Levi, D. (1927), Brit.J.Surg.: 15: 282.

Levy, R.L., (1924), Arch.Int.Med.: 33: 742.

Malgaigne, J.F., (1841),
"Oevres Completes d'Ambroise Paré". Paris: 3: 555.

Mekie, E. and Miller, H., (1929), Brit.Med.J.,: 1: 244.

Morris, N. and Graham, S., (1931), Arch.Dis.Child.: 6: 237.

Mottram, V.H., and Graham, G., (1940),
"Hutchison's Food and the Principles of Dietetics".
9th.Edition, London. 625.

Murphy, J.B., (1909), J.Amer.Med.Assoc.: 52: 1248.

Mutch, N. and Ryffel, J.H., (1913), Brit.Med.J.: 1: 111.

McLendon, J.F., Cavett, J.W. and Johnson, R., (1937),
J.Lab. and Clin.Med.: 22: 1000.

McNealy, R.W. and Willems, J.D., (1929),
Surg., Gynaec. and Obstet.: 49: 794.

McNealy, R.W. and Willems, J.D., (1931), Arch.Surg.: 22: 649.

Nakazawa, F., (1925), Tohoku J.exper.Med.: 6: 130.

Osborne, E.D., (1922), J.Amer.Med.Assoc.: 79: 615.

Parkes, F.W., (1904), Brain: 27: 170.

Pasteur, W., (1904), Lancet: 1: 1418.

Perusse, G.L., (1932), Surg.Gynaec. and Obstet.: 54: 770.

Peskind, S., (1924), J.Met.Research: 6: 207.

Peskind, S., Rogoff, J.M. and Stewart, G.N., (1924),
Am.J.Physiol.: 68: 530.

Peyer: quoted by Gros.

Pressman, J.J., (1930), Am.J.Med.Sc.: 179: 520.

Ramazini: quoted by Gros.

Reach, F., (1902), Arch.f.exp.Path.u.Pharm.: 47: 231.

Reznikoff, P., (1929), J.Am.Med.Assoc.: 93: 367.

Rose, M.S., (1912),

"A Laboratory Hand-Book for Dietetics". New York.

Rubino and Varela (1922), Klin.Wochenschr.: 2: 2370.

Satta, (1905), Bietr. z.chem.Physiol.u.Path.: 6: 376,

(quoted by Carpenter).

Scott, E.L. and Zweighaft, J.F.B., (1932),

Arch. Int. Med.: 49: 221.

Scudi, J.V. and Ratish, H.D., (1938),

J. Lab. and Clin. Med.: 23: 615.

Sennest: quoted by Gros.

Short, A.R. and Bywaters, H.W., (1913), Brit.Med.J.: 1: 1361.

Sorensi, A.L., (1935), M.Rec.: 141: 435.

Still, G.F., (1931), "History of Paediatrics". London. 139.

Stubbs, S.G.B. and Bligh, E.W., (1931),

"Sixty Centuries of Health and Physick", London. 20.

Tallerman, K.T., (1919), Quart.J.Med.: 13: 356.

Thoburn, T.W. and Hanzlik, P.J., (1915),

J. Biol. Chem.: 23: 163.

Thomson, J., (1827),

"The Works of William Cullen". Edinburgh. 2: 409.

Turrel, R., Marino, A.W.M. and Nerb, L., (1940),

Ann. Surg.: 112: 417.

Valesquez, B., (1939), Prenza med.argent.: 26: 958.

Van Slyke, D.D., (1924), J.Biol.Chem.: 58: 523.

Varela and Rubino, (1922), Med.Klin.: 26: 831.

Voit, C. and Bauer, J., (1869), Zeitschr.f.Biol.: 5: 536.

Von Tornack, J., (1938), Klin.Wochenschr.: 17: 1400.

Wood, E.H., (1941), Canad.Med.Assoc.J.: 44: 592.