TABLE IV.—Incidence of Isolation of *Bact. coli* O 111 from Rectal Swabs at Similar Periods in Control and Trial Groups

Day:	0	1-2	3-4	5-6	7-8	9-10	11-13
Control series:							
No. of swabs ..	30	11	25	10	15	12	18
No. positive for <i>Bact. coli</i> O 111 ..	30	11	23	9	14	10	16
Percentage positive ..	100	100	92	90	93	83	89
Trial series:							
No. of swabs ..	26	17	25	25	9	23	24
No. positive for <i>Bact. coli</i> O 111 ..	26	15	18	12	5	4	6
Percentage positive ..	100	88	72	48	56	17	25

period for which cases in the control series were positive for *Bact. coli* O 111 was 22 days; in the treated series it was 14 days.

These results suggest that the administration of chloramphenicol was associated with a moderate reduction of the total *Bact. coli* flora and a more striking reduction in the isolation rate of *Bact. coli* O 111. It is worthy of note that all except one of the trial group became negative for *Bact. coli* O 111 on one or more occasions during the days when chloramphenicol was given, but 11 of these became positive again shortly after the end of treatment.

Discussion

The dangers to the life and health of young babies which result from their admission to hospital are well known, and usually follow the development of respiratory, gastro-intestinal, skin, or mucous membrane infections. Epidemic diarrhoea is often the most serious of these infections, and may carry a high mortality, especially in babies who are already debilitated by their primary illness. In our experience during the past three years, in Liverpool, there has been a fairly close correlation between bacteriological cross-infection with *Bact. coli* O 111 and the development of gastro-enteritis. In addition, certain clinical features such as loss of weight and anorexia may be observed before the onset of diarrhoea, and often before the rectal swab is positive for *Bact. coli* O 111.

In spite of the application of the measures recommended for the prevention and control of cross infections (Medical Research Council, 1951) we have experienced from time to time small outbreaks of diarrhoea and vomiting. Our experience with chloramphenicol in established gastro-enteritis has been encouraging enough to warrant the trial of this drug as a prophylactic agent. Though in an attempt to obtain representative control and treated cases we used as the criterion the appearance of *Bact. coli* O 111 in the stools, this was done only because at the time there was a clear association between cross-infection with *Bact. coli* O 111 and the onset of diarrhoea. We do not suggest that this is always so. In other circumstances the value of prophylactic chemotherapy would be much more difficult to assess. The administration of chloramphenicol is not a substitute for other precautions, but is an additional measure which might be tried when the generally accepted methods for control of cross-infection have failed.

No toxic effects from chloramphenicol have been observed with a dosage of 75 mg. per lb. (165 mg. per kg.) per day for seven days, but it is probable that a lower dosage for a rather longer period might prove equally effective. Three of our cases which received chloramphenicol developed mild diarrhoea 3, 4, and 10 days after the drug had been discontinued, and rectal swabs were positive for *Bact. coli* O 111 during this period. In the light of this experience we suggest that chloramphenicol should be given for 10 to 14 days in a daily dosage of 50 mg. per lb. (110 mg. per kg.).

The bacteriological data, though compatible with the suggestion that *Bact. coli* O 111 may be the cause of one form of infantile gastro-enteritis, are equally explicable on the basis that their occurrence is non-specific and that their suppression during treatment with chloramphenicol is merely a reflection of the general effect of this drug on the *Bact. coli* group. In our experience, so far, the occurrence

of *Bact. coli* O 111 has been so closely associated with the disease that we have felt that infants cross-infected with this organism should be closely observed for prodromal signs of gastro-enteritis.

Recent experience with small numbers both of clinical cases of gastro-enteritis and of those cross-infected with *Bact. coli* O 111 suggests that sulphadiazine may be as effective as chloramphenicol.

The prophylactic use of chloramphenicol or sulphadiazine is not considered necessary when isolated cases of cross-infection (both clinical and bacteriological) arise, but in the presence of widespread cross-infection not prevented by the usual measures the use of these drugs may be valuable.

Summary

Chloramphenicol was given to alternate patients in a consecutive series of 56 infants under 1 year who became cross-infected with *Bact. coli* O 111 after admission to hospital. The results in this small series suggest that this antibiotic might be of value in preventing the development of clinical gastro-enteritis.

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TESTS FOR GLYCOSURIA

A COMPARISON OF BENEDICT'S TEST, CLINITEST, AND GLUCOTEST

BY

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Benedict's qualitative test is extensively used in clinical medicine, but its accuracy depends on the correct proportions of urine and Benedict's solution and on heating without "bumping" for the correct time. While these form no obstacle in a laboratory, many years' experience in our large diabetic clinic has shown how dubious the results may be when the test is performed by nursing staff, medical officers, and practitioners not connected with the clinic. Reducing substances have been found to be absent in innumerable urines referred to us for confirmation of a positive Benedict test found elsewhere. Such errors have been diminished but not eliminated by heating for five minutes in a boiling water-bath instead of two minutes over a flame.

In recent years the detection of reducing substances in urine has been simplified still further by the commercial production of tablets containing copper sulphate, sodium hydroxide, citric acid, and sodium bicarbonate in such proportions that when a tablet is dissolved in a measured amount of diluted urine enough heat is generated by solution of the sodium hydroxide, and by neutralization of part of it with the citric acid, for reduction of the copper to take place, giving green, yellow, or orange cuprous oxide colours, just as in Benedict's test. Such a test has many advantages, for with the commercial set of tablets a glass dropper is provided of such a size that the requisite volume is given by 5 drops of urine and 10 drops of tap-water. Under these conditions

the amount of heat is constant and adequate, and independent of the dexterity of the manipulator. The reaction is complete in less than a minute, and a semi-quantitative assessment of any glucose present may be made by comparison with a suitable colour chart. Such a tablet test would be of great value if it could be proved to be comparable in sensitivity and specificity to the Benedict test. Comparable sensitivity is of special importance, so that the traces of reducing substances present in normal urine may not be shown, but that slight increases of pathological importance may be detected.

It was decided, therefore, to compare the qualitative results given by two of the tablet tests—namely, the "clintest" and the "glucotest"—with the results given by Benedict's test and with those of the quantitative determination of glucose in a series of 300 urines, mainly from diabetic patients.

Methods

The clintest and glucotest were performed as recommended by the manufacturers. The screening test suggested in the instructions provided with the clintest outfit, in which urine is not diluted with water, has not been investigated.

Benedict's quantitative method for the estimation of glucose in urine is widely used, but it is the experience of one of us (H. R. M.) that the accuracy of the determination is seriously impaired when the glucose content is less than 2 g. per 100 ml.—that is, when the 25 ml. of Benedict's quantitative reagent requires for its titration more than 2.5 ml. of urine—and especially is this so when the urine is concentrated. For this reason glucose in urine has been more accurately determined in the present experiments by the method of Folin and Wu, after suitable dilution of the urine with water to bring the glucose content within the range 100–200 mg. per 100 ml. The validity of this procedure depends on the accuracy of the diluting technique and on the assumption that the non-glucose-reducing substances estimated by the Folin-Wu technique were not unduly concentrated in urine. With the Folin-Wu method, the mean non-fermentable-reducing substances in 17 urines have been found to amount to 0.031 ± 0.005 g. per 100 ml. (range 0.01–0.05 g. per 100 ml.). These amounts have been ignored because in assessing the significance of our results the urines have been regarded as groups differing in their glucose content by at least 0.1 g. per 100 ml.

Results

The Table shows the recoveries obtained by the Folin-Wu method when glucose was added to various urines containing between 0.1 and 3 g. of glucose per 100 ml. of urine.

Recoveries Obtained by the Folin-Wu Method When Glucose was Added to Various Urines Containing Between 0.1 and 3 g. of Glucose per 100 ml.

Amount of Glucose Added (g./100 ml.)	No. of Urines Examined	Recovery		
		Mean (g./100 ml.)	S.D.	Range
0.5	8	0.49	0.05	0.43–0.59
1.0	16	0.99	0.09	0.82–1.12
2.0	16	1.99	0.17	1.65–2.30
2.5	4	2.56	0.10	2.46–2.66
5.0	4	5.14	0.15	4.94–5.29

Although in no way equal to the regularly excellent recoveries shown by the Folin-Wu method when glucose is added to blood, they appear to be accurate enough for the present purpose.

In the Chart the results of the examination of the 300 urines by the three tests have been grouped according to their glucose content as determined by the Folin-Wu method. The results with the three qualitative techniques have been separately plotted as block diagrams with the results of the test as abscissae and the number of urines

Chart showing results of examination of 300 urines by Benedict's test, the clintest, and the glucotest.

giving those individual results as ordinates. The grading of the results as 0, trace, +, 2+, 3+, and 4+, following the usual arbitrary convention in which 4+ represents complete reduction of the reagent, was read by comparison with the colour chart. The number of urines examined in each group is included.

Discussion

Under ideal conditions—namely, with pure glucose solutions—there should be an exact correlation between the quantitative interpretation of the qualitative tests and the amount of glucose. All solutions containing less than 0.1 g. per 100 ml. might be expected to give no measurable reduction, all solutions containing 0.1–0.2 g. a trace result, 0.2–0.4 g. a + result, etc. All solutions containing more than 2 g. per 100 ml. would be expected to give a 4+ result. On the other hand, in practice, urines would not be expected to give such a proportionate response, not only because of the presence of interfering substances but also because of the arbitrary grading of the results. It is obvious from the Chart that this has been found.

Inspection of the results given by urines containing 0–0.1 g. of glucose per 100 ml. shows that the clintest and glucotest are slightly less sensitive than the Benedict method. This is confirmed by the results with urines containing 0.11–0.2 and 0.21–0.4 g. of glucose per 100 ml. These last results also show that the glucotest is considerably less sensitive than the clintest, because 15 of 50 urines containing 0.21–0.4 g. of glucose per 100 ml. gave a negative result with the glucotest. Within the range 0.41 and 1.5 g. the results given by the three tests are not obviously different, and the grading of the quantitative response visually does not always correlate well with the quantity of

glucose present. Thus in urines containing 0.61–0.8 g. all three tests gave results varying from a trace to 3+. Glucose concentrations over 2 g. per 100 ml. usually, but not always, caused complete reduction in each test. Such discrepancies are likely to be due to the presence in individual urines of substances interfering with the sensitivity of the test as well as to the difficulty of visual assessment of partial reduction. Difficulty was sometimes experienced with the colour charts used with the glucotest for grading the results. The colours did not always accurately represent those observed in actual tests. In this respect the clintest colour chart seemed superior.

It is likely that Benedict's test, when properly performed, is the most satisfactory of the three tests because of its slightly greater sensitivity. However, the simplification and convenience of the tablet technique make it the method of choice in almost all circumstances, certainly in the control of treatment of known diabetics, either in the clinic or by the patient in his home, as well as in the routine testing of urine, whether before operation or in illness generally. In the control of treatment of diabetes, failure to detect an occasional trace or to determine the exact percentage of glucose is of little significance. The routine Benedict test in illness or before operation is seldom well performed because of the difficulties of accurate measurement of reagent and urine and because of the practical difficulties of uniform heating; the much simpler and more readily standardized tablet test is to be preferred, although it is slightly less sensitive. The value of the tablet test in life assurance examination is a problem requiring separate investigation. Most of the subjects are symptomless and may not excrete more than traces of glucose, which might be missed by the tablet test and detected by Benedict's test. Perhaps a screening test using undiluted urine would be advantageous in this respect.

Two serious disadvantages of the tablet test require mention. First, the tablets are highly caustic and should be tipped into the tube, if possible without handling them. Secondly, although the tubes of tablets as manufactured are stable for many months, once the tubes have been opened it would appear that the inside of the cap is disturbed so that the bottle is not completely air-tight. A number of clinicians have reported deterioration in the tablets (turning blue) after only a few weeks, even though the stopper has been replaced tightly. The manufacturers might well effect some improvement in this respect. This would also be an advantage to the patient performing his own urine tests at home: the tablets are so often kept in the humid atmosphere of the bathroom. The manufacturers should describe a suitable method of cleaning the tubes after use. Water alone is not always satisfactory, and a preliminary rinse with acetic acid (vinegar by the patient), followed by water and drying, might be recommended.

The time saved by use of the tablet technique is of special importance. Benedict's test can seldom be done in less than 10 minutes by persons not trained in the laboratory. This allows for measuring two solutions, boiling, standing, and washing out the tube. In the tablet method there is one measurement and the result is read after 15 seconds, thus saving at least five minutes of time for each test. In a hospital of 500 beds with out-patients, an average of 100 routine urine tests a day is not an excessive estimation, and replacement of Benedict's test by the tablet test will save about nine hours of working time each day.

It must be emphasized that a positive result with a tablet test requires just the same consideration in regard to non-glucose-reducing substances as Benedict's test—that is, when the positive test is not accompanied by clinical signs of diabetes the reduction needs to be proved by the customary methods to be due to glucose and not to other reducing compounds.

From the diabetic angle, all that is usually needed is to know whether the urine contains no sugar, a little, or a lot. The three tests investigated show this equally well.

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INTRACRANIAL HYPOTENSION ASSOCIATED WITH SUBDURAL HAEMATOMA*

BY

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The first clear account of intracranial hypotension was given by Leriche (1920) in patients with severe cranio-cerebral injuries. Further examples of the syndrome were described (Leriche and Wertheimer, 1921; Leriche and Emery, 1922), and later Leriche (1931) said that the syndrome was seldom recognized and that although there was nothing absolutely characteristic in the symptomatology it formed a striking clinical entity.

Since these early descriptions of the syndrome from Strasbourg, most of the literature of the condition has come from the Continent, mainly from French authors. It was the subject of a joint discussion at a combined meeting of the Société de Neurologie de Paris and the neurological section of the Royal Society of Medicine in 1948 (*Proc. roy. Soc. Med.*, 1948), when it was clear that most of the British members present were unfamiliar with the condition, at any rate in its severe forms.

Most of the reports of the more severe forms of the syndrome have come from neurosurgical clinics, and apart from the minor manifestations such as lumbar puncture headache, it must be regarded as a rare occurrence in the province of a physician. This paper records the only two examples of the condition which I have recognized and treated, and both followed the drainage of fairly large subdural haematomata. Subdural haematoma seems to be associated with intracranial hypotension much more often than any other space-occupying lesion, so far as can be judged from the published reports. For example, Krebs, Puech, and Brunhes (1937) reported six cases of hypotension with ventricular collapse, of which two followed the drainage of subdural haematomata, one of an extradural haematoma and one of an arachnoid cyst following head injury. Lalonde and Gardner (1948) reported nine cases, of which seven followed the drainage of a subdural haematoma, one followed the removal of a pituitary adenoma, and one of a parasagittal meningioma. Chorobski (1950) also records six cases, one with a post-haemorrhagic cyst and one with both extradural and subdural haematomata. Gloor (1951) mentions its association with three cases of subdural haematoma in a series of 23 cases of widely different neurological conditions.

The association of a low cerebrospinal fluid pressure with subdural haematoma and chronic intracerebral haematoma is well known and is indeed an important diagnostic feature in these conditions. It is not so well recognized, however, that the persistence of the "low-pressure state" following the surgical drainage of the haematoma, and its association with severe cerebral symptoms, possibly of greater degree than those preceding operation, is responsive to simple therapeutic measures such as the intrathecal injection of normal saline to restore the pressure to a normal level, the intravenous injection of hypotonic saline or distilled water, or the inflation of the ventricles with saline or air. In

*Based on a paper read to the West Midlands Association of Physicians on May 26, 1951.