if considerable differences in nutrition do occur between the children in the various schools, where milk and meals are provided, or in their homes, where the dietary is both uniform and adequate as a result of equitable rationing during the past nine years. The mothers who were approached regarding their own age at the menarche were drawn from favoured social groups, and it is unlikely that the mothers' nutrition differed greatly from that of their daughters. It is unfortunate that the planning of a similar inquiry among mothers in poorer homes would probably be hampered by prejudices associated with the subject.

The figures in Table III confirm the conclusion of Ellis (1948) that the stage of sexual maturity is as important in assessing growth as is chronological age. It is noteworthy that no entry relating to the age of the menarche is at present included in the new school medical record card of the Ministry of Education. If the physical growth of girls is to be adequately assessed this omission will need to be remedied.

Shuttleworth (1937) presents individual growth curves of 10 girls who first menstruated between 10 years 7 months and 11 years 3 months, and of 10 girls with menarche between 14 years 5 months and 15 years 2 months. The first group were on the average taller during the period from $8\frac{1}{2}$ to 12 years of age than those in whom the menarche occurred later. There was a rapid decrease in rate of growth in stature after the menarche. Those whose menarche was later continued to grow after the girls in the earlier group had practically ceased and in the end were taller. Our findings do not confirm this last observation. Table V summarizes the figures of Table III for the 47 girls

TABLE V.—Mean Heights and Weights of Girls aged 17 and 18 According to Age of the Menarche

Age of the Menarche	No. of Girls	Mean Height	Mean Weight
Under 13 years ..	10	64.4 in.	125.4 lb.
13-14 ..	13	64.6 in.	135.7 lb.
14-15 ..	13	64.3 in.	119.9 lb.
15 years and over ..	11	65.1 in.	125.4 lb.
All ages ..	47	64.6 in.	126.8 lb.

aged 17 and 18. There is no consistent tendency for those whose menarche was later to be either taller or heavier than those who first menstruated earlier.

Conclusions

Data concerning the age of the menarche were obtained from 1,338 girls (604 of whom had not yet started their periods), between the ages of 10 and 19, attending three secondary schools in Oxford City and six in Oxfordshire. These schools cater for children from a variety of social and economic environments.

1. No differences in the age of onset of menstrual periods could be detected between children attending the town and country schools. The median age (that at which half of the girls had started menstruating) was 13.6 years. The age ranged in individuals from 9 to 18 years.

2. Girls who have not started menstruating are considerably shorter and lighter than their fellows of the same age whose periods have started. On the other hand, there is little difference in the mean heights and weights of the latter groups when subdivided according to the interval since the menarche. It is concluded that there must be a considerable spurt in growth before or around the age of menarche.

3. The close relation with height and weight means that information on the age of menarche is essential for the adequate assessment of physical growth in adolescent girls.

As yet no provision is made for this information on the Ministry of Education's new school medical record card. This omission should clearly be made good.

4. A small number of mothers of a more favoured social group were compared with their children in respect of the age of menarche. There was no apparent tendency for the children to start menstruating at an earlier age.

5. It is suggested that the negative findings (1) and (4), which fail to confirm the work of earlier investigators, may arise from the comparable nutritional status before or during adolescence, in this country, of the groups involved.

6. There is no evidence that the height and weight of girls aged 17 and 18 is in any way related to the age at which they first menstruated.

We are indebted to the educational and medical authorities and the teaching staffs of nine schools in the City and County of Oxford, to Dr. Isabelle Little in particular, and to the mothers of the girls for their help in obtaining the necessary data.

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OBSERVATIONS ON THE TREATMENT OF INFANTILE GASTRO-ENTERITIS

BY

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The aetiology of infantile gastro-enteritis is still far from clearly understood. In a proportion of cases met with in Malta, especially in our hot summers, the disease is almost certainly of infective origin, but the nature of the causative organisms is a matter of acute controversy, as it has been impossible to incriminate any specific agent except in some cases belonging to the dysenteric, enteric, and salmonella group of diseases. Bacteriological examination of the stools of healthy and sick babies has disclosed no qualitative differences; indeed, some paediatricians have held that gastro-enteritis was not provoked by any specific organism but that it originated from the invasion of territory normally sterile, such as the upper reaches of the small intestine (Moro, 1916; Blacklock *et al.*, 1937). Others have postulated a virus infection and offer as evidence the observation that epidemics of gastro-enteritis and of colds seem often to occur together (Gunn, 1944). From the study of some 400 cases Sevitt (1945) concludes that paracolon and proteus bacilli are responsible for many cases of infantile gastro-enteritis. The disease may not represent a single entity, but may be the resultant of a number of different agents.

An Explanation of the Mechanism of Enteritis

If the rapid and abundant loss of fluid which is the cardinal sign of gastro-enteritis originates from the intestinal vascular plexus it must imply quite an abnormal permeability of the capillaries. Although many factors may contribute to produce this exaggerated leakage, it is probable that histamine ranks high on the list.

Histamine is a disintegration product of the amino-acid histidine, and the conversion can be effected by a variety of organisms acting on proteins; appreciable quantities of histamine are found in the stools of mammals. Experimentally, if administered in suitable amounts it is able to induce vomiting and diarrhoea, often with strong colicky pains. The effect is transitory owing to a rapid destruction of histamine by various agents, among which is the ferment histaminase, and perhaps also by a compensatory discharge of adrenaline (Feldberg, 1941).

Analysis of Some Methods of Treatment

If one bears in mind how many different methods of treatment have been proposed for enteritis, most of which are successful in at least some cases, one can reason that it is by no means essential to kill any pathogenic organisms in order to cure the disease.

Castor oil will often clear a mild diarrhoea in a matter of hours, and it can do so only by the rapid excretion of the irritating agents; its antiseptic powers are of course negligible. If we are prepared to admit that histamine is the principal cause of the diarrhoea, then its quick removal lowers its concentration around the intestinal vascular plexus, thus diminishing the permeability of the blood vessels. The natural resistance of the body can then cope with the organisms remaining in the gut.

Heisler (1928) and Moro (1929, 1930) recommended apples for enteritis. This treatment was widely conceded to be effective in mild cases, and various modifications, such as the use of bananas and carrots, were proposed by Continental paediatricians (Feer, 1929; Fanconi, 1930; and Glanzmann, 1939). The mode of action is supposed to be due to the adsorption of toxic and irritating agents by pectin (Salomon, 1936). Ramos (1941) published a study on the carob (*Ceratonia siliqua*), a tree of the Leguminosae family which is abundant in most Mediterranean countries. The pod, whose epicarp is almost as hard as wood, contains a sweet pulp much prized as fodder for horses. Ramos claims that roasted and pulverized carob pulp is very effective in gastro-enteritis.

While apples are rich in pectin (5.7 g. per kg. of apple pulp), a kilogram of a 10% carob suspension contains only 1.8 g. of this carbohydrate: hence the active material in the carob pulp cannot be pectin. Martin du Pan (1945a), who states that carob pulp is very rich in lignin, ascribes its therapeutic action to this. Freudenberg (1939) has written an interesting paper on this hydrophilous colloid, while Martin du Pan (1945b) states that one litre of a 5% carob suspension is able to adsorb 0.74 g. of histamine, whereas a 5% suspension of "aplona" (an apple product) is able to adsorb little more than half this quantity. On adsorption the amino-acids are not susceptible to the action of bacterial enzymes, and thus the formation of histamine and other irritants is much diminished.

The First Antihistaminic

In 1930 Best and McHenry reported that watery extracts of various organs were able to inactivate histamine through the action of a body to which they gave the name of histaminase. Rose and Browne (1938) thought that, although histaminase was not the only agent capable of destroying histamine, they had found that the mucosa of the small intestine contained large quantities of histaminase; it was therefore possible that in the absence of sufficient quantities of this enzyme histamine would display its usual toxic effects. Histaminase is believed to act on histamine by first separating ammonia from the side chain and

then finally cracking the ring nucleus containing the two atoms of nitrogen and the three atoms of carbon.

Some years before the last war histaminase was marketed by the I. G. Farbenindustrie under the name of "torantil." Great hopes were entertained on its curative action in gastro-enteritis and in allergic conditions, and encouraging reports by Rigler (1936), Horster (1936), and others were published, but subsequent papers by Miller and Piness (1940) and others have been much less optimistic, so that the drug has now been practically forgotten.

Limitations of Sulpha Drug Therapy

It cannot be denied that some cases of gastro-enteritis do get well spontaneously, especially when the diarrhoea is so profuse that the toxic products are so diluted that they are rendered harmless. The dilution is further assisted when the fluid intake, oral or parenteral, is increased. There are several reports on the good results obtained from the use of sulpha derivatives in gastro-enteritis (Anderson, 1941; Meyer, 1943), but it is common experience to find them useless in some of the severer cases (Hinden, 1948). This can be explained by admitting that if the permeability of the intestinal vascular plexus exceeds a certain critical value, then death through dehydration may occur even in the presence of an efficient sulpha drug capable of killing any causative organisms. It is obvious that no sulpha derivative can neutralize or otherwise dispose of previously formed histamine or related bodies. It is recognized that sulpha drugs are also ineffective in non-specific diarrhoeas due to virus or other unrecognized pathogens.

Antihistamines in Gastro-enteritis

Starting from the assumption that histamine was the immediate cause of the fatal dehydration found in gastro-enteritis and was responsible for many of the toxic manifestations, it was decided to treat a number of cases with an antihistamine ("benadryl" in this series) combined later with a sulpha derivative. Moderately severe and severe cases only were selected, and the criteria were: the presence of pyrexia of 101° F. (38.3° C.) or over in the rectum; more than eight stools a day; and the presence of toxæmia, as shown by the rapid pulse, dyspnoea, and prostration. Vomiting, although present in the majority of cases, was not a constant finding.

The results are given in three Charts. In Chart 1 are included 24 cases treated by a short period of starvation during which half-normal saline or Hartmann's sodium lactate solutions were used orally, or Hartmann-Ringer solution parenterally. After 18 to 24 hours a proprietary buttermilk was given in gradually increasing amounts. No other medicinal measures were used. Four babies died, which gives a lower mortality than is usual in hospital cases; all cases were treated in private homes.

In Chart 2, 16 cases are reviewed, and these received the same treatment as before but with the addition of

CHART 1.—Showing daily average number of stools in 24 cases treated by a short period of starvation during which various solutions were given.

benadryl. Parenteral infusions were not required. Although rapid diminution in the number of stools was observed the fever was often uninfluenced and the condition of some patients deteriorated when the benadryl was stopped. When a sulpha derivative was concurrently administered rapid and permanent improvement set in.

CHART 2.—Showing daily average number of stools in 16 cases treated as in Chart 1 but with benadryl and combined benadryl and sulpha drug added.

ably sulphadiazine (Klose, 1947) and sulphamezathine. Blatt and his associates (1947) could discover no significant difference between the action of sulphathiazole and phthalylsulphathiazole. It is my impression, based on the observation of over 120 cases, that there is little to choose between sulphamezathine and phthalylsulphathiazole, and I always use one or the other of these two drugs.

As regards the dose of benadryl, I give 1 mg. for every month of age four-hourly, and when improvement sets in the same dose every six hours. This dosage is suitable for babies up to 5 months of age. From 6 months to 1 year the dose is 6 to 8 mg., administered in the same way.

CHART 3.—Showing daily average number of stools in 42 cases treated with sulphamezathine alone (dotted line) and in 40 cases treated with sulphamezathine and benadryl (continuous line).

Vomiting, when present, ceases in a very short time; the prostration, dyspnoea, and tachycardia subside in most cases in a few hours. The continuous and irritating whine is replaced by a more peaceful cry; this is not surprising, as benadryl seems to have a sedative effect on the central nervous system, and in certain cases infants who have been unable to sleep owing to restlessness or colic repose quietly after a few doses. In no case was it necessary to resort to the parenteral administration of fluid; in fact, four cases among those treated showed a moderate but clearly visible generalized oedema. That this represents water retention is shown by a rapid increase of weight—as much as 200 g. or more in two or

three days. The general condition of the patients is excellent, and the swelling subsides when the benadryl is stopped or the intervals between the doses are lengthened. There was only one death in the series treated with sulphamezathine and benadryl, but three deaths occurred in the series treated with sulphamezathine alone.

Conclusion

This communication is of the nature of a preliminary report, and further studies are necessary to assess the value of the combination of antihistamines and sulpha derivatives in the treatment of infantile gastro-enteritis. It is claimed that this combination does influence and materially shorten the course of the disease. Should this claim be confirmed some progress in the treatment of a distressing and often fatal condition will have been achieved.

Summary

The symptomatology of infantile gastro-enteritis can be explained, at least in part, as a manifestation of histamine intoxication.

The beneficial action of various therapeutic measures can be considered as being due to the removal or neutralization of histamine by rapid evacuation, by adsorption, or through antihistamines. Sulpha drugs, by acting on pathogenic organisms, may prevent the formation of histamine.

These measures often fail when the histamine intoxication is severe unless they destroy the histamine *in situ* or prevent the histamine from acting on the intestinal vascular plexus; only antihistamines can do this.

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The Ministry of Health states that the latest figures for nursing and midwifery staffs in hospitals in England and Wales under the National Health Service continue to increase. In March of this year there were 5,600 more nurses than six months earlier, the total being 137,600. This figure includes 21,600 part-time workers—2,600 more than in September, 1948. The number of student nurses increased by 2,578 to 45,300 in the same period. The numbers of full-time midwives in hospitals rose from 4,381 to 4,813, pupil midwives from 3,184 to 3,677, and part-time midwives from 809 to 888. In the same six months full-time domestic staff increased from 99,733 to 100,514 and part-time from 23,131 to 25,065.