CONCLUSION

The results shown in the treatment of cancer of the breast by radium, x-ray, and surgery, tend to favour the irradiation method in preference to radical surgical procedures in all groups of cancer of the breast. Especially is the irradiation method indicated in Groups II and III, and even in Group I the percentage is comparable with surgical procedures.

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A FURTHER REPORT ON THE ASCORBIC ACID TREATMENT OF WHOOPING COUGH*

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IN a previous communication[6] two of us (M.J.O. and B.M.U.) gave an account of the treatment of 10 cases of whooping cough with ascorbic acid (synthetic vitamin C). While the small number of cases forbade any statistical conclusions they nevertheless did show that this treatment had an almost specific effect in decreasing the intensity and duration of the disease. At the time of forwarding the above paper we believed this to be an entirely new system of treatment, but we have since discovered that Otani[7] had published his results in treating 81 cases of whooping cough with ascorbic acid, and we take this opportunity of acknowledging his priority and confirming his results. His method of treatment was the intravenous injection of the same brand of ascorbic acid (Redoxon-Hoffmann-La Roche) as we have used orally, and his patients were drawn from hospital clinics, while ours were treated in the home. He does not give much detail in the paper but his general conclusions are matched by ours. In hospital work the intravenous method may be ideal, but where oral use is possible and efficient, as it is here, we believe the greater simplicity and reduced cost (about one-fifth that of the intravenous method) of our method is more suited to general practice.

In the present communication we present the results in 17 additional cases of whooping cough treated by oral administration of ascorbic acid. An attempt was made to gain a more accurate idea of dosage and utilization of the vitamin by studying its urinary excretion before and during treatment. There is only a limited capacity for storage of the vitamin in the body, and excess is rapidly excreted by the kidney. When first seen many of the patients were excreting almost no ascorbic acid; others of slightly better financial circumstances showed small amounts, but still below normal figures. As treatment was begun the excretion of the acid rose, and when saturation of the tissues was complete there was a sharp well-maintained rise in excretion of the acid. Cured cases responded like normal cases; small additional amounts added to the usual intake caused corresponding rises in urinary values. Our first 5 patients were given the vitamin all in one dose each day, but this proved to be a poor method. According to Widenbauer,[10] such administration leads to excretion of large amounts in the urine, but does not give a true saturation of the tissues. Accordingly, our other patients were given the vitamin in divided doses daily, which gave much better excretion curves and a more accurate estimation of the degree of saturation of the body. The technique of the urinary estimations, and some of the graphs obtained, as carried out by one of us (F.D.W.), are given below.

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The technique adopted was that of Harris and Ray,[5] slightly modified. This technique involves the analysis of the total 24-hour excretion of urine, the urine being preserved with 10 per cent of its volume of glacial acetic acid, and analyzed within 12 hours of voiding. When patients (and, in particular, children) are being treated in their own homes it is no easy matter to ensure that the total output is obtained over a period of 14 to 21 days, while the cost of the glacial acetic acid required is by no means a negligible matter. As the patients we were treating were all receiving daily large amounts of ascorbic acid it seemed to us that analyses of single urinary specimens, voided at the same time each day, would under the circumstances give us as much information regarding the comparative ascorbic acid excretion as would a 24-hour specimen. Accordingly, we decided to analyze the first sample of urine voided each day, and made arrangements for this to be collected in bottles containing a known amount of glacial acetic acid, the amount of acid being calculated to ensure that it was at least 10 per cent of the total volume. The samples were all analyzed within three to four hours by titration with dichlorphenol-indophenol. The specificity of this method of estimation has been questioned by Wacholder and Hamel,[9] Ferrand and Policard[4] and others, but the wide acceptance of this method, its simplicity from a routine standpoint, and the fact that we were not concerned with the exact ascorbic acid content of the urine so much as with the comparative rise and fall in the titration values during therapy, influenced us in adhering to it.

Our primary consideration being the adoption of a method of estimation which, while being reasonably accurate, could be carried out easily by clinical technicians, we used the Hoffmann-La Roche dichlorphenol-indophenol tablets. One tablet, containing 0.002 g. of the sodium salt, was dissolved in 50 c.c. of distilled water, and 1 c.c. of this solution (equivalent to 0.02 mg. ascorbic acid) was used for the titration. The dye solution was made up freshly every 3 days. Otherwise, the details were strictly in accordance with the recommendations of Harris and Ray.

Typical results are shown graphically in Charts 1 and 2.

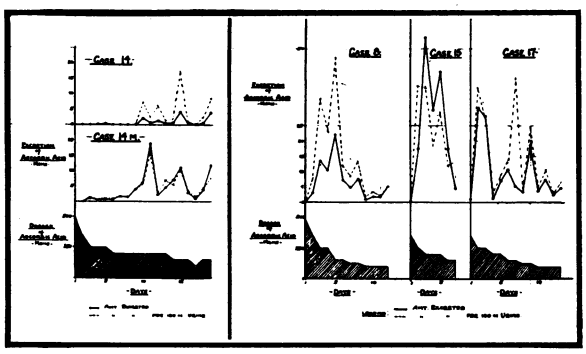

Chart 1 Chart 2

Chart 1.—Case 14 is a 7 months old infant on the breast. Case 14m is the mother. Therapy to mother.
Chart 2.—Typical responses to routine dosages of ascorbic acid.

Our plan of dosage was modified from that of Widenbauer[10] in which large "loading" doses are given for a short time and then the daily dosage is reduced during the remainder of the time. Our first few cases were started with too high dosage, and this proved wasteful. We finally adopted the following routine of daily dosage: 350, 250, 250, 200, 200, 150, 150, 125, 125, 100, continuing at the 100 mg. level until the case was complete, or stopping the dosage at any stage at which there was a complete remission of symptoms for two days. The average total dose was about 2,700 mg. We disregarded both age and weight of the patient, preferring to simplify the method by making routine tables of dosage. As even excessive doses of the vitamin do not produce undesirable effects, owing to rapid excretion of excess, and since the cost of the medication is very reasonable this method seemed best adapted for use by the general practitioner. Where a large number of patients are to be treated, as in institutional work, this scale of dosage might perhaps be reduced slightly, but there is a definitely increased demand for vitamin C in whooping cough, and we prefer to over-supply rather than under-supply this need.

Where a case does not respond to this routine dosage experience has taught us to inquire into the amount actually taken by the patient. Thus, in one case where urinary analyses and clinical reports fluctuated wildly, we found that the mother had dissolved the daily dose in a quart of milk and that the dosage depended upon how much of the milk was taken by the child. As a rule, parents are only too glad to administer the medication faithfully as soon as they find that better sleep for the whole family is the result. The ascorbic acid is in the form of tablets, combined with lactose, and will dissolve easily in water, milk or fruit juices, or it may be eaten like a candy, as it has a not unpleasant sour taste.

A patient on routine dosage who shows a sudden drop in urinary excretion, even when medication is taken, usually shows a corresponding change in the clinical picture. The development of the whoop seems to use up a large amount of vitamin. This would appear to strengthen Brown's[1] suggestion of a pertussis toxin which has an affinity for nervous tissue, and particularly since Otani[7] has shown that vitamin C has a definite antagonistic action on the toxin from the Bordet-Gengou bacillus. Where whoop develops during the treatment the dosage may be increased slightly for a few days if desired, but we find that the whoop is mild and soon disappears under the routine dosage.

Cases are reported briefly below.

CASE 1

F., 7 years. Day cough 12 days; night cough 10 days; no whoop or vomiting. Urinary ascorbic acid less than 0.3 mg./100 c.c. Dosage, 500 mg. every second day for 3 doses, then daily doses averaging 200 mg. Day cough marked 8 days, slight 6 days; night cough marked 2 days, slight 4 days. No whoop. Slight vomiting for 3 days about a week after beginning treatment. Duration of disease, 15 days; total amount of drug, 3.0 g.

CASE 2

M., 6 years. Day cough 7 days, night cough 4 days; no whoop or vomiting. Urinary ascorbic acid less than 0.2 mg./100 cc. Treated similarly to Case 1, but with smaller doses. Day cough marked 6 days, slight 3 days; night cough marked 3 days, slight 3 days. No whoop or vomiting. Duration of disease, 9 days; total dosage, 2.0 g.

CASE 3

F., 2½ years. Day cough 7 days, night cough 6 days; no whoop or vomiting. Urinary ascorbic acid less than 0.2 mg./100 c.c. Preliminary dosage 250, 250, 500 every second day, then daily doses averaging 150 mg. Day cough marked 5 days, slight 9 days; night cough marked 5 days, slight 3 days. No whoop or vomiting. Duration of disease, 14 days. Total dosage, 2.25 g.

CASE 4

F., 6 years. Day cough 11 days, night cough 7 days; whoop 4 days, no vomiting. Urinary ascorbic acid 1.0 mg./100 c.c. Treatment, 500 mg. daily for 3 days, then daily doses averaging 200 mg. Day cough marked 12 days, slight 2 days; night cough marked 3 days, slight 2 days. Whoop marked 10 days, slight 2. Slight vomiting on 4th, 6th 7th, and 8th days. Duration of disease, 14 days; total dosage, 3.1 g.

CASE 5

F., 6½ years. Day cough 7 days, night cough 5 days, whoop 1 day, vomiting 1 day. Urinary ascorbic acid 1.9 mg./100 c.c. Treatment, 500 mg. on first day, then doses averaging 175 mg., daily. Day cough marked 4 days, slight 8 days; night cough stopped from the first. Whoop marked 1 day, slight 9 days. Slight vomiting on the 4th, 5th, and 6th days. Duration of disease, 12 days; total dosage, 1.97 g.

CASES 6 AND 7

These cases were uncontrolled by attendants and varied so widely that they are not reportable with the others of this series.

CASE 8

F., 3 years. Day cough 5 days, night cough 2 days. No whoop. Vomiting 1 day. Urinary ascorbic acid 0.37 mg./100 c.c. The remainder of the patients in the series were given dosage regularly and in divided doses, and urine specimens were from the first voiding in the morning. Dosage here, 500, 350, 250, 250, 150, 125, 125, then 100 mg. daily. Day cough marked 8 days, slight 10 days; night cough marked 3 days, slight 12 days. No whoop. Vomiting slight, only on 6th to 15th days. Duration of disease, 18 days; total dosage, 3.0 g.

CASE 9

M., 7 yrs. Day cough 4 days, night cough 4 days; no whoop or vomiting. Urinary ascorbic acid less than 0.2 mg./100 c.c. Treatment as for Case 8. Day cough almost incessant at first; attacks greatly reduced in number in 3 days, remained marked for 7 days, slight for 8 days. Night cough marked 5 days, slight 9 days. No whoop or vomiting. Duration of disease, 18 days; total dosage, 3.0 g.

CASE 10

M., 6 years. Day cough 21 days, night cough 21 days; no whoop; vomiting 2 days. Urinary ascorbic acid 1.7 mg./100 c.c. Treatment as for Case 8. Day cough 15 times daily at start; 12 attacks each for next two days, then about 5 per day for next 6 days, then 2 slight coughs daily for 5 days. Night cough marked 3 days, slight 5 days. No whoop. Slight vomiting 6 days. Duration of disease, 14 days; total dosage, 2.85 g.

CASE 11

M., 5 years. Day cough 7 days, night cough 3 days; whoop 1 day, no vomiting. Urinary ascorbic acid 1.58 mg./100 c.c. Therapy, 500, 350, 150, 150, 150, 125, 125, then 100 daily. Day cough 12 times daily at start for 2 days, then 5 the next day, then slight cough 15 days. Night cough, 6 attacks for first two nights, then only slight for 10 days. Whoop once daily for 5 days, slight 8 days. Slight vomiting on 6th and 11th days. Duration of disease, 18 days. Total dosage, 2.82 g.

CASE 12

F., 25 years. Day cough 21 days, night cough 12 days; no whoop; vomiting 7 days. Urinary ascorbic acid 0.97 mg./100 c.c. Therapy, 375, 250, 200, 200, 150, 150, 150, 125, 125. Day cough 6 on first day, none on second day, then 7, 4, 2, and none on following days. Night cough none on first night, 3 second night, none thereafter. Vomited only once, on 3rd day. Duration of disease, 6 days; total dosage, 1.72 g.

CASE 13

F., 36 years. Day cough 21 days, night cough 21 days; whoop 14 days, no vomiting. Urinary ascorbic acid 1.45 mg./100 c.c. Therapy, 500, 350, 250, 150, 150, 125, 125, 100, 100, 100. Day cough marked 4 days, then stopped abruptly. Night cough 3 on first night, then none thereafter. Whooping once on 2nd and 4th day only. No vomiting. Duration of disease, 4 days; total dosage, 1.95 g.

CASE 14

F., 7 months, on breast. Day cough 4 days, night cough 2 days; no whoop or vomiting. Urinary ascorbic acid less than 0.3 mg./100 c.c. As child was still on breast, ascorbic acid was given to mother (Case 14m) so that ample amounts would be excreted in the milk. Day cough marked 5 days, slight 6 days; night cough marked 4 days, slight 2 days. 1 slight whoop on first day, then none. No vomiting. Duration of disease, 11 days.

CASE 14M

F., 26, (mother of Case 14). No symptoms. Urinary ascorbic acid less than 0.5 mg. per 100 c.c. Therapy, 500, 350, 250, 250, 250, 200 daily for next 8 days, then 150, 150, 150, 100, 150, 150. Total dosage, 4.05 g. (see Chart 1).

CASE 15

M., 3½ years. Day cough 10 days, night cough 10 days; no whoop or vomiting. Urinary ascorbic acid 0.85 mg./100 c.c. Therapy, 350, 250, 200, 200, 200, 150, 150. Day coughs 4 on first day, 1 on second day, 2 on third day, thereafter none. Night cough, 2 on first night, thereafter none. No whoop or vomiting. Duration of disease, 3 days; total dosage, 1.5 g.

CASE 16

F., 3½ years. Day cough 3 (?) days, night cough 14 days; no whoop; vomiting 3 days. Urinary ascorbic acid 2.9 mg./100 c.c. Therapy, 350, 250, 250, 200, 200, 150, 150, 150, 150, 125, 125, then 100 mg. daily. Day

cough 15 on first day, night cough 7; whoop 1; vomited 22 times. Second day, 3 day coughs, 7 night coughs; 1 whoop; 10 vomitings. Third day, 2 day coughs, 7 night coughs; 3 whoops; 2 vomitings. Day cough marked for another 2 days, then slight for 8 days. Night cough marked 3 days, slight 4. Whoop none after 3rd day. Slight vomiting on 4th, 5th, 7th and 8th days. Duration of disease, 13 days; total dosage, 2.57 g.

CASE 17

M., 3 years. Day cough 14 days, night cough 10 days; no whoop; vomiting 7 days. Urinary ascorbic acid 1.0 mg./100 c.c. Therapy, 350, 250, 250, 200, 200, 150, 150, 125, 125, 100 daily thereafter. First day, 12 day coughs, 8 night coughs; no whoop; 20 vomitings. Second day, 6 day coughs, no night cough or whoop; 2 vomitings. Thereafter, day cough marked 5 days, slight 2 days; night cough, whoop and vomiting, none. Duration of disease, 9 days total dosage, 2.3 g.

CASE 18

F., 17 months. Day cough 3 days, night cough 2 days; no whoop or vomiting. Urinary ascorbic acid less than 0.5 mg./100 c.c. Therapy similar to Case 17. First and second days, 15 day coughs, 12 night coughs; 1 whoop each day. Third day, 1 day cough, 2 night coughs; no whooping or vomiting. Thereafter, day cough slight 6 days, night cough; whoop and vomiting, none. Duration of disease, 9 days; total dosage, 2.35 g.

CASE 19

M., 2½ years. Day cough, 7 days; night cough 3 days; no whoop or vomiting. Urinary ascorbic acid 0.65 mg./100 c.c. Therapy, 350, 250, 250, 250, 250, 200, 200, 150 mg. thereafter. Day cough over 20 for each of first two days; night cough, same; no whoop or vomiting. Thereafter, day cough marked (12 to 16 attacks daily) for 8 days, then slightly less numerous and less intense for 10 days. Night cough marked for 5 days, slight for 7 days. Slight whoop on 9th to 14th days. Slight vomiting on 3rd, 7th, 8th and 9th days. Duration of disease, 15 days; total dosage, 2.95 g. This case proved the most resistant of all our series. Urinary analysis showed that the medication was taken faithfully, and we have no explanation, other than a possibly overpowering amount of toxin as shown by the severity and number of coughs, for the long delay in improving the symptoms. However, when the patient did respond the symptoms improved rapidly.

In the case reports, we have used the word "slight" to show various modifications of the symptoms. Slight cough indicates a short loose cough without any considerable respiratory embarrassment. Slight whoop denotes a shortened and more quiet type than usual. Slight vomit indicates that there is no true vomiting, in the sense of expulsion of gastric contents, but rather the expectoration of mucus. We have accepted as the duration of the disease the time required for the complete or almost complete arrest of the symptom which tends to remain longest in whooping cough—the day cough. Even with this standard, the average duration for 15 children above is only about 13 days. The two adults were cured in 4 and 6 days, respectively.

Clinical changes occurred in the following order. (1) Marked reduction or complete arrest of vomiting; (2) reduction or disappearance of night cough; (3) reduction in number or intensity of whoop; (4) reduction in number or intensity of day cough.

We consider a case cured when whoop, vomiting and night cough have disappeared, and the day cough is present, if at all, in very slight form. Urinary analysis serves as a guide also: a cured case responds to a small additional dose by a corresponding rise in the urinary excretion of ascorbic acid. In many cases we have continued the administration of 100 mg. for a few days after the symptoms had subsided. Occasionally some of the patients have a short (2 to 3 days) exacerbation of the symptoms after treatment is stopped, and this small additional administration serves to prevent it.

The change in the general condition of the patients is rapid and clearly noticeable. Due possibly to better rest, they soon become much more lively in habit. Appetite improves from the first. The change from a child who fears to undergo any exertion because of the prolonged coughing spell and possible vomiting that ensues, to a child who plays about with only an occasional irritative cough is gratifying to both parent and physician.

Cases 14 and 14m are worthy of special mention. Case 14 is that of a 7 months old infant still on the breast, and Case 14m is the mother. For a suckling infant to have whooping cough is most unusual as, according to Correns,[2] Wacholder,[8] and Ferdinand,[3] ample amounts of ascorbic acid for a growing infant are excreted in human milk, even a year after delivery of a child. On inquiry, we found that the mother in this case had deleted fresh fruits from her diet because she found they produced colic in the child. Titration of her urine showed an almost complete absence of ascorbic acid, and hence an almost complete depletion of her body stores of vitamin C. Widenbauer[11] states that a pregnant woman requires two and one-half times the normal dosage of ascorbic acid from the third month on, and a lactating woman requires double the normal amount, of which half is excreted in the milk. Accordingly, we kept the mother's dosage at higher levels for a longer period than usual, and in another case of the same type would increase our scale of dosage still more. The infant's excretion of ascorbic

acid remained minimal until the mother began to excrete appreciable amounts in her urine. From this point on the child's excretion rose parallel with the mother's, and clinical improvement corresponded. We believe other nursing mothers may have had this same difficulty with fruits in the diet, and suggest the administration of ascorbic acid as an easy way out of the difficulty, as no unwanted digestive disorder occurred in the child following its use.

Case 15 shows an excellent response to therapy in a moderate case. Here, day and night cough of 10 days' duration responded to 3 days' treatment by complete remission, without recurrence.

Very little difference in the average daily need of vitamin C is shown between adults and children. Widenbauer[11] estimated daily intake and excretion of ascorbic acid in normal persons over a period of weeks, and found the requirement for an adult to be 27 to 28 mg. per day more than the amount excreted in the urine. A normal child of 3 years showed a requirement of 21 to 22 mg. per day over excreted amounts. The same author shows that the taking of thyroid also raises the requirement of vitamin C, and so, possibly, the difference in weight between adult and child may be almost compensated for by the more rapid metabolism of youth. Harris and Ray[5] administer 600 mg. of ascorbic acid to adults as a test for hypovitaminosis-C, so that our "loading" dose of 350 mg. in a child does not seem out of place, particularly as we find C-unsaturation as an almost invariable occurrence in whooping cough.

A word may be ventured as to dietary sources of vitamin C. Samples of orange juice have been estimated by various investigators to contain from 10 to 20 mg. of ascorbic acid per ounce. Oranges thus prove, at least in this part of the country, to be at least two or three times as expensive a source of the vitamin as the brands of ascorbic acid now on the market. Milk is hopelessly inadequate as a source of vitamin C, as, according to Correns,[2] pasteurized milk, even in midsummer when green feed is plentiful for cows, contains only 1.26 to 1.91 mg. per 100 c.c. Even unpasteurized milk, after standing 24 hours, contains very small amounts. Widenbauer,[10] investigating children in hospital in Danzig on standard or special diets, (according to illness), found that practically all of them were lacking in vitamin C, although there were no cases of scurvy among them. Evidently, hypovitaminosis-C may be of much commoner occurrence than has been considered hitherto, and as long as it is not severe enough to show as clinical scurvy may pass unrecognized unless chemical investigation of urinary ascorbic acid is carried out.

CONCLUSIONS

1. Chemical examination of the urine shows varying degrees of hypovitaminosis-C in whooping cough.

2. Saturation of whooping cough patients with ascorbic acid decreases markedly the intensity, number and duration of the characteristic symptoms.

3. A simplified routine for such treatment is described, as used by us in this series of cases of whooping cough.

We wish to express our thanks to Messrs. Hoffman-La Roche for supplying us with the ascorbic acid ("Redoxon") used in these cases.

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PATHOGENESIS OF ACUTE GLAUCOMA.—A. Brav is dissatisfied with most of the theories advanced on this subject. He believes that acute glaucoma is caused by increasing pressure on Schlemm's canal from hypertrophy of the ciliary processes. The proper use of optical corrections, which had been prescribed first before the age when prodromal symptoms might be expected, would prevent the onset of this condition. Eserine, by pulling upon the ciliary body, and iridectomy, by producing a cyclodialysis, both release pressure on the canal of Schlemm.—*Med. Rec.*, June 2, 1937, p. 447. Abs. in *Brit. M. J.*