

LETTERS TO THE EDITORS

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Inhibiting Action of some Analogues of Folic Acid on the Growth of Plant Tumours

ANALOGUES of folic acid have been found capable of inhibiting the growth of the Rous sarcoma in chickens¹ and sarcoma 180 in mice², of causing a remission in leukæmic children³ and of prolonging the survival of leukæmic mice⁴. The effect of twelve of these analogues (all samples of folic acid and its analogues were kindly supplied by Lederle Laboratories, Pearl River, New York) on the growth of tumours induced by the crown gall bacterium on carrot tissue has been tested. Cylinders of tissue 10 mm. diameter × 6 mm. high were removed as described in a previous communication⁵, and inoculated with virulent crown gall bacteria. Four days later, when the first signs of tumour formation became visible along the line of the cambium, 0.05 ml. of a 1/1,000 solution of the folic acid analogue to be tested was dropped on to, and spread over, the surface of the tissue. The amount of substance applied was 0.05 mgm. per fragment. Sterile distilled water was applied to the control group. Twenty carrot fragments were used in each test. The accompanying table shows the percentage of fragments which had developed macroscopically visible tumours four weeks after treatment had been applied.

Percentage of carrot fragments with macroscopically visible tumours 4 weeks after treatment with 0.05 mgm. of folic acid analogues

Compound	% Tumours	Compound	% Tumours
4-amino-PGA	0	N ¹⁰ -methylpterioic acid	90
4-amino-N ¹⁰ -methyl-PGA	0	9-methyl-PGA	100
4-amino-9, N ¹⁰ -di-methyl-PGA	0	4-aminopteroyl aspartic acid	90
4-amino-9-methyl-PGA	0	4-aminopteroyl- <i>dl</i> -2-alanine	100
4-aminopteroyl- γ -glutamyl- γ -glutamyl glutamic acid	0	4-aminopteroyl- <i>dl</i> -threonine	90
Pteroylaspartic acid	100	Pteroylglutamic acid (folic acid)	100
Pteroyl- <i>dl</i> -aspartic acid	100	Control	100

Five compounds, issued by Lederle Laboratories under the names 'Aminopterin', 'A-methopterin', 'A-denopterin', 'A-ninopterin' and 'Amino-teropterin', were thus found capable of suppressing completely the growth of tumour tissue induced on carrot by inoculation with crown gall bacteria, at a dosage level of 0.05 mgm. per fragment. The tumour tissue which had begun to form frequently turned brown and was probably killed. A dose of 0.0005 mgm. of these substances very greatly reduced tumour growth. At this low dosage-level the inhibition could be partially reversed by the addition to the solution of 10 mgm. per ml. of folic acid. Details of these reversal effects and a description of the comparative action of these compounds on tumour and non-tumour tissue will be published elsewhere.

It is of interest that all five compounds which proved capable of inhibiting growth of crown gall tumour tissue have also been shown to inhibit the growth of several animal tumours⁶. This finding suggests a fundamental similarity between the folic acid metabolism of the plant and animal cell. It also

suggests that carrot fragments on which tumours have been induced by crown gall bacteria may provide convenient test objects for the screening of compounds for their tumour-inhibiting action.

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R. S. DE ROPP

New York Botanical Garden,
New York 58, N.Y.

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⁴ Burchenal, J. H., Burchenal, J. R., Kushida, M. N., Johnston, S. F. and Williams, B. S., *Cancer*, **2**, 113 (1949).

⁵ de Ropp, R. S., *Nature*, **162**, 459 (1948).

⁶ Stock, C. C., personal communication.

Hæmogram, Serum Protein and Plasma Volume of Healthy, Well-nourished East Africans in Uganda

IN the course of an investigation on anæmia in Kampala, Uganda¹, it was found necessary to establish standard hæmatological and other values to enable the investigator to assess the degree of recovery. It was found that these values were the same as had been found in Europeans^{2,3,4}, North Americans⁵ and Indians⁶, the only exception being the albumin/globulin ratio.

The subjects were fit male adults belonging to the African upper class. They were county and district chiefs, ministers and other high officials in the Buganda Native Government, students and nursing orderlies. These men, thirty-four in all, could afford to eat as much food as they wanted, though, with the exception of the students, they were living mainly on a vegetarian diet. The thirteen students who consumed meat and milk regularly were compared with fourteen of the other subjects, of whom it was made reasonably certain that they were near-vegetarians. There was no significant difference between the two groups in the hæmogram and in the value for total serum protein. But in the students, serum albumin was significantly higher (P.E.D. < 0.0001) and the globulin correspondingly lower (P.E.D. < 0.04). In the whole group of thirty-four subjects, there was a negative association between albumin and globulin levels, the coefficient of correlation being -0.7.

All subjects wore shoes regularly and were thus protected against massive hookworm infestation. Of twenty-two who permitted their stools to be tested, eleven showed no hookworm ova, although several samples were investigated and the concentration method was used. The eleven hookworm carriers did not differ from the eleven non-hookworm carriers in their hæmatological and serum protein values. Six hookworm carriers agreed to be purged, and the hookworms removed never exceeded fifty. There was no alteration in the hæmogram following the 'worming'. Eight of the thirty-four volunteers were carriers of the sickle cell trait; they did not differ from the rest in their hæmogram. This was to be expected, as in a mass survey⁷ in Uganda no correlation had been found between anæmia and sicklæmia. The incidence of the sickle cell trait in a given population depends on its tribal composition rather than on its state of health⁸.