Major R. F. Flint, National Research Council of the United States; Arctic, Desert and Tropic Information Center, Army Air Forces, New York.

Dr. L. M. Gould, National Research Council of the United States; Chief of the Arctic Section, Arctic, Desert and Tropic Information Center, Army Air Forces, New York.

Group Captain W. F. Hanna, Department of National Defence for Air, Ottawa.

Dr. D. Jenness, Department of Mines and Resources, Ottawa.

Dr. H. L. Keenleyside, Department of External Affairs, Ottawa.

Dr. T. Lloyd, Department of Geography, Dartmouth College, Hanover, N. H.

Commander D. B. MacMillan, USN. Hydrographic Office, Washington.

Dr. R. Newton, President of the University of Alberta, Edmonton.

Dr. J. J. O'Neill, Department of Geological Sciences, McGill University, Montreal.

G. R. Parkin, Sun Life Assurance Company of Canada, Ltd., Montreal.

Commander G. A. Patterson, USN. Hydrographic Office, Washington.

Dr. V. Stefansson, 67 Morton Street, New York.

Lt. A. L. Washburn, Arctic Section, Arctic, Desert and Tropic Information Center, Army Air Forces, New York.

Ensign J. C. Weaver, USNR, Hydrographic Office, Washington.

Col. J. T. Wilson, Director of Operational Research, National Defence Headquarters, Ottawa.

Dr. V. C. Wynne-Edwards, Department of Zoology, McGill University, Montreal.

Until further announcement, communications should be addressed to L. M. Gould, Carleton College, Northfield, Minnesota.

RICHARD FOSTER FLINT

YALE UNIVERSITY
(*On leave of absence*)

SPECIAL ARTICLES

IMPAIRMENT OF RESPONSE TO STILBESTROL IN THE OVIDUCT OF CHICKS DEFICIENT IN L. CASEI FACTOR[1] ("FOLIC ACID")

SEVERAL experimental and clinical studies have indicated a close relationship between the metabolism of the estrogens and the vitamins of the B-complex.[2,3,4,5] Stilbestrol[6] normally induces a marked proliferation of the tissues of the genital tract. This is reflected in an increase in weight of the genital organs which may be employed as an index of stilbestrol activity.

We have found that large doses of stilbestrol elicit only a slight weight increase in the oviducts of chicks maintained on a diet deficient in *L. casei factor* (L.C.F.). However, a marked weight increase is observed in the oviducts of control chicks receiving L.C.F. supplements either curatively or prophylactically. Moreover, pantothenic acid deficient chicks show substantial oviduct responses to stilbestrol.

New Hampshire Red chicks were maintained from hatching on the purified diet and supplement described by Campbell *et al.*[7] L.C.F. was administered by dropper either as the aqueous solution of crystalline material or as a concentrate. All estrogen-treated chicks received 0.5 mgm of stilbestrol in 0.1 cc of corn oil subcutaneously on each of the six days preceding autopsy.

The data (Table 1) show a striking difference between the oviduct weights obtained after stilbestrol administration in the L.C.F.-deficient chicks and in

TABLE 1

OVIDUCT WEIGHT RESPONSE TO STILBESTROL IN L.C.F. AND PANTOTHENIC ACID DEFICIENT CHICKS.*

	No. of Chicks	Oviduct mgms mean	Oviduct mgms range	Body wt. gms mean	Body wt. gms range
20 γ cryst. L.C.F. daily from birth	9	450	309–777	140	111–166
20 γ cryst. L.C.F. daily last 10 days	12	196	84–474	110	59–158
No L.C.F.	16	62	32–82	71	53–90
10 γ eq. L.C.F. conc. daily from birth	15	462	200–666	125	108–158
10 γ eq. L.C.F. conc. daily last 10 days	14	184	90–457	107	69–170
No Pantothenic; 10 γ eq. L.C.F. conc. daily from birth	9	281	156–553	70	60–80

* All chicks 21 to 25 days old at autopsy; oviduct weights of 13 uninjected chicks of the same age averaged 25 mgms (range 19–33) and their body weights averaged 117 gms (range 97–144 gms).

[1] The term "*L. Casei Factor* (L.C.F.)" refers to that member of the "folic acid" group isolated by B. C. Hutchings, E. L. R. Stokstad, N. Bohonos and N. H. Slobodkin (SCIENCE, 99: 371, 1944) and found by them to be active in the nutrition of the chick. This material was kindly furnished by Lederle Laboratories through the courtesy of Dr. E. L. R. Stokstad.

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the supplemented controls. This difference obtains whether the L.C.F. supplement is administered from hatching or only as a curative measure during the last ten days preceding autopsy.

In the curative experiments there was considerable variability in the degree of therapeutic effect as evidenced by increase in body weight. The stilbestrol response varied accordingly, thus reducing the mean oviduct weight for the group as a whole. Nevertheless, the restorative effect of the administered L.C.F. on the oviduct response is apparent.

The pantothenic acid deficient chicks showed a growth failure quite comparable to that observed in the L.C.F. deficient animals. Despite this marked effect, they exhibited a good response to stilbestrol, indicating that debility and limitation of growth are not sufficient, *per se*, to effect the reduction in oviduct response observed in the L.C.F.-deficient chicks.

The normal response to stilbestrol stimulation is characterized by a substantial increase in the thickness of the muscular and mucosal layers of the oviduct. Gross examination of the oviduct of the stilbestrol treated L.C.F.-deficient chick reveals that the small weight increase over the normal may be attributed to accumulation of fluid in the lumen and that the walls of the oviduct remain thin and translucent.

The data indicate that an adequate intake of *L. casei* factor is essential for the normal metabolism of stilbestrol in the chick. This finding is an interesting example of the interdependence of a dietary trace substance and a hormone-like factor and further emphasizes the importance of adequate nutrition for normal endocrine function.

ROY HERTZ
W. H. SEBRELL

U. S. PUBLIC HEALTH SERVICE,
NATIONAL INSTITUTE OF HEALTH

INHIBITION OF METAL CATALYSIS AS A FUNGISTATIC MECHANISM

MECHANISMS of action for chemicals that inhibit growth of or are lethal to microorganisms are little understood. Knowledge of positional effects of various atomic groupings is extensive, and general mechanisms are frequently cited, including protein precipitation, enzyme inactivation, inhibition of respiration. However, specific cases are rare for which the *modus operandi* of inhibitory or lethal action is known. Possible exceptions are the sulfonamide antagonism,[1,2] the blocking of enzyme surfaces by adsorption of heavy metals to the active areas,[3] and the inhibition of the -SH group by $HgCl_2$.[4]

The fact that microorganisms require traces of several metal elements indicates that these elements are involved in catalytic processes in the cells; *i.e.*, that the metals function as part of one or more enzyme systems.[5] Hence a chemical capable of precipitating the metals in such enzyme systems should prevent growth of microorganisms by inhibiting metal catalysis, particularly if metals are precipitated in the form of chelate inner complex salts which are non-electrolytes. 8-hydroxyquinoline forms such chelate salts with many metals,[6] and is also an efficient fungistatic and bacteriostatic compound.[7,8] It is suggested that the latter property is the result of the former. This theory for the mechanism of fungistatic action of 8-hydroxyquinoline was tested biologically in the following ways:

(1) At lower pH values (in general, below pH 3.5) complex formation does not take place between 8-hydroxyquinoline and certain metals,[9,10] including several considered essential for growth of fungi: copper, manganese, iron and zinc. Hence the chemical should not be fungistatic at lower pH values as essential metal ions should be available. Flasks of Tochinai nutrient solution (1.5 g. KH_2PO_4, 0.5 g. $MgSO_4$, 10 g. Bacto Peptone, 20 g. C.P. Maltose, 1,000 ml distilled water), in pH series, were inoculated with three test fungi (*Fusarium oxysporum* f. *lycopersici*, *Ceratostomella ulmi* and *Penicillium* sp.). Normal growth was found to occur at low pH values in the presence of as much as 100 mg of 8-hydroxyquinoline per liter (Table 1), a dose far in excess of that causing complete inhibition at higher pH levels.

TABLE 1

EFFECT OF pH ON FUNGISTATIC ACTION OF 8-HYDROXYQUINOLINE

	Average weight (mg) of Penicillium mat at pH:					
	2.2	2.5	3.2	3.8	4.5	5.7
Nutrient plus 100 mg of 8-hydroxyquinoline per liter	378	260	111	0	0	0
Nutrient alone	390	401	347	352	311	184

The effect of increasing acidity is not merely to neutralize the weak basic properties of 8-hydroxyquinoline. Neither is the compound destroyed at low pH values.

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