"that venous thrombosis is initiated by an injury of the vessel wall which causes a localized liberation of tissue thromboplastin to produce a clot attached to the area of injury."⁴ There is more evidence against than in favour of this theory. Tissue thromboplastin is an intracellular particulate substance, and cellular destruction, therefore, is necessary to release it. Further, the difference between thrombosis and intravascular coagulation has by now been well established. If Dr. Quick's theory was correct one would not expect venous thrombosis in factor VII deficiency cases. We have, however, observed post-operative thrombo-embolism in two patients with total factor VII deficiency.⁵

Platelets play a major role in the first stages of thrombus formation. Since the discovery of adenosine diphosphate⁶ as a key-factor at this stage and the significance of the platelet surface clotting systems for the progression and consolidation of the platelet thrombus it seems more profitable to pursue this line of investigation along with studies on plasma coagulation. —I am, etc.,

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Goitre in Klinefelter's Syndrome

SIR,—A nodular goitre is reported as an incidental finding at post-mortem of a 71-year-old male with chromatin-positive Klinefelter's syndrome (March 30, p. 866). That this is not in fact a mere coincidence is suggested by many similar reports in the literature, summarized by Burt *et al.*¹ No information is available whether these individuals fall into the chromatin-negative group of Klinefelter's syndrome or whether they have a female sex chromatin pattern and an XXY chromosomal constitution. Recently Davis *et al.*² reported that three of four XXY individuals studied had an abnormally low radio-iodine uptake. An editorial³ in the same issue refers to the importance of the differential incidence of common diseases in individuals of abnormal chromosomal constitution and the light that this might throw on aetiological factors. In a recent study,⁴ one of 12 infertile males with non-toxic nodular goitre, treated surgically, was shown to be of XXY chromosomal constitution. On the other hand none of 23 males with primary thyrotoxicosis whose sex chromatin was studied showed a female pattern.

It would seem likely, therefore, that at least non-toxic nodular goitre, a disease more characteristically present in females, is more frequent in XXY individuals than in normal males.—I am, etc.,

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Antibiotic Growth Stimulation

SIR,—In response to the consideration of my work in your annotation on "Antibiotics as Human Food Supplements" (December 15, 1962, p. 1594) and the letter on "Antibiotic Growth Stimulation" (Dr. M. Lev, February 23, 1963, p. 539) I suggest that evidence for direct modes of action does not exclude stimulation by antibacterial action and vice versa. The direct and indirect effects may be synergistic and are certainly not mutually exclusive. An action established for micro-organisms in the intestinal tract does not necessarily delineate the effect upon the mucosal cells which are a part of a more highly organized system, and the establishment of an action upon the host cells does not necessarily preclude a different action upon the microbial cells.

In 1946 Peter Moore, E. B. Hart, C. A. Elvehjem, and I discovered the phenomenon of antibiotic growth stimulation.¹ By typical interdepartmental co-operation with the Department of Bacteriology of the University of Wisconsin we were able to present evidence for the antibacterial action. We discussed this and noted: "The possibility that these agents are acting systemically cannot be overlooked."

Several years later the discovery of commercial potential in the effect² led many investigators to the question of the mode of action. We³ began germ-free animal experiments with antibiotics on December 1, 1950. Streptomycin showed no clear effect. The first experiment with terramycin at 25 mg./kg., showed a positive response in germ-free chicks ($P < 0.001$). Knowing that a wide range of levels was effective in classic (conventional) chicks, we doubled the quantity of antibiotics in subsequent experiments. The results were negative. The next month a series of experiments was begun with low levels of antibiotics. The results were positive. The data,³ showed that the "high" level of antibiotics gave no stimulation while the "low" level stimulated growth ($P < 0.001$) in germ-free chicks. No definitive experiment has been reported in the decade since our germ-free work. While several groups have verified our results⁴⁻⁶ with high levels, none seem able to break the "barrier" to try 10–15 mg. antibiotic per kg. diet.

Stress is an important factor in the interpretation of the results. On some farms antibiotics have no effect; on others, a dramatic effect is shown. Unless the proper experimental conditions are provided for the effect, a thousand negative results carry little weight.

The evidence for a direct action is summarized.⁷ Results with germ-free chicks and poult fed low levels of antibiotics were verified by Nickell,⁸ who showed the stimulation of germ-free plants by antibiotics. Growth stimulation is found in conventional chicks with non-bactericidal compounds—that is, arsenicals, detergents, inactivated antibiotics, and a variety of dyes. Many micro-organisms have been shown to be stimulated by sub-inhibitory doses of antimicrobial agents.

Further evidence is the fact that the growth stimulation of antibiotics is only one part of the total picture. The broad view is given in a concept termed *hormoligosis*⁷ (from the Greek *hormo*, meaning to excite, and *oligo*, meaning small quantities). The generalized hypothesis states that any inhibitory agent, when administered in quantities substantially lower than the minimum inhibitory quantity, can be stimulatory to the organism. In recent studies on the action of antibiotics