crystalline biotin on yeast. We have not yet determined the lower limit of effectiveness, though we have found concentrations up to 1γ per cc to be harmless and little better than the more dilute solutions. The extreme dilution at which the vitamin is effective accounts for our failure to inactivate yeast by long heating under pressure at an alkaline reaction; the vitamin is not completely destroyed under such conditions and sufficient remains to be effective. The insolubility in absolute alcohol of the effective factors in the dried yeast is probably apparent only. That the vitamin and not some contaminant is the effective agent would seem to follow from the dilutions at which the vitamin is used and because the contaminants are probably not the same in the synthetic and natural products, both of which are effective.

The beneficial effects of yeast on the growth of the root tips is not completely accounted for by the vitamin B_1 content of the yeast, since the growth in White's solution containing yeast is better than in the same solution in which the yeast is replaced by vitamin B_1. Part of the beneficial effect of the yeast is due to the ash elements in it, since growth is improved by the addition of yeast ash to White's solution in which the yeast is replaced by vitamin B_1 and the growth in the latter solution is improved also by the addition of supplementary mineral elements. We have not yet determined whether amino acids, hormones or vitamins other than B_1 present in yeast play a significant rôle in the cultivation of excised tomato root tips.

Our results show that excised tomato roots grow if supplied with water, oxygen, mineral salts, carbohydrate and vitamin B_1. These results are similar to those of Schopfer[7] for *Phycomyces Blakesleeanus* which he has found requires vitamin B_1, though this organism apparently requires asparagine also in addition to mineral salts, carbohydrate and the vitamin. It appears that a medium containing mineral salts, carbohydrate and vitamin B_1 is adequate for the unlimited growth of tomato roots. We have grown excised tomato roots successfully for five months in such a medium through four subcultures without evident diminution in growth rate. Such a medium is composed of known constituents and may be regarded as a synthetic medium adequate for the growth of tomato roots.

Whether any substitute for vitamin B_1 can be found remains to be determined. Present evidence indicates that pantothenic acid (a highly purified sample furnished the writers by R. J. Williams) can not be substituted for vitamin B_1. Another aspect of the problem of general interest and significance is the possible occurrence of vitamin B_1 in highly purified sugars. Judging from the response of excised tomato roots, growth factors (probably vitamin B_1) are present in samples of purified maltose and dextrose secured from various companies. Hall, James and Stuart[8] have reported the occurrence of growth stimulants for yeast in white sugar, and Schopfer[7] found a growth factor for *Phycomyces* in maltose.

Our results confirm the working hypotheses originally formulated to explain the beneficial action of yeast on the growth of excised roots in a mineral solution containing sugar and demonstrate that the parasitic relationship of the tomato root to the top involves both carbohydrate and vitamin B_1.

Whether the medium the writers have used is adequate for all types of plant tissue remains to be seen; the results, however, are significant in presenting a synthetic solution apparently adequate for the growth of one type of plant tissue and should be of interest to those engaged in the cultivation of isolated plant embryos and other portions of higher plant tissues.

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THE SIGNIFICANCE OF THE ADRENALS FOR ADAPTATION[1]

IN the course of our studies on the alarm reaction[2,3] we found that the symptoms of adrenal deficiency are almost identical with those observed in non-adrenalectomized animals after exposure to serious damage. Decreased blood pressure; accumulation of water in tissues, with a simultaneous loss of water from the blood; decreased blood sugar; decreased body temperature; muscular weakness; formation of gastric and intestinal ulcers; are the most characteristic features both of adrenalectomy and of the alarm reaction. We have to conclude, therefore, that there is no specific change characteristic of adrenal deficiency, and that the changes observed after the removal of the adrenals are simply due to the response of the organism to general damage—that is to say, they are changes caused by the alarm reaction. We found, furthermore, that alarming stimuli (*i.e.*, stimuli which would elicit an alarm reaction) will cause much more pronounced changes in adrenalectomized animals than these same stimuli would be able to produce in the normal. This

[7] W. H. Schopfer, *Ber. deut. bot. Ges.*, 52: 308–313, 1934.

[8] H. H. Hall, L. H. James and L. S. Stuart, *Jour. Ind. and Eng. Chem.*, 25: 1052–1054, 1933.

[1] A detailed publication of the experimental data mentioned in this letter will shortly appear in the "Archives Internationales de Pharmacodynamie et de Thérapie."

[2] H. Selye, *Can. Med. Assoc., Jour.*, 34: 706, 1936; *Nature*, 138: 32, 1936; *Brit. Jour. Exper. Pathol.*, 17: 234, 1936; *Endocrinol.*, in press.

[3] H. Selye, C. Harlow and J. B. Collip, *Endokrinol.*, 1936.

in itself suggested that the function of the adrenals is to increase the resistance of the organism to alarming stimuli; furthermore, we observed that a marked enlargement of the adrenals is a constant result of exposure to damaging stimuli, an observation which corroborates the assumption that these glands play an important rôle in the defence of the organism against alarming agents.

It has been claimed that the adrenal is particularly important for the maintenance of normal body temperature, for the prevention of fatigue following exhausting muscular exercise, for the detoxification of various harmful substances and for the maintenance of a constant blood sugar level. Exposure to variable surrounding temperature, excessive muscular exercise, toxic doses of various drugs or agents apt to cause hypoglycemia, act as alarming stimuli. Consequently a decreased resistance to such agents is to be expected if we assume that the function of the adrenals is to prevent the damaging effects of the alarm reaction. But this evidence was not sufficiently conclusive to justify such a theory. We therefore proceeded to experiment with a large number of rats which we adapted to cold, muscular exercise or various drugs. Since damaging agents cease to elicit an alarm reaction after adaptation has occurred, we could expect this experiment to show whether the damage caused by a certain stimulus in an adrenalectomized animal is the result of the stimulus as such or of the alarm reaction which it produces. We found that animals previously adapted to such stimuli as muscular exercise, cold or toxic doses of drugs will tolerate exposure to these same stimuli very well, even after the adrenals have been removed, while exposure to the same stimuli invariably kills not-adapted, adrenalectomized controls, with symptoms characteristic of adrenal insufficiency and of the alarm reaction.

We concluded from these observations that one of the most important functions of the adrenals is to increase the resistance to alarming stimuli. Since most stimuli are "alarming" when the organism is first confronted with them, the adrenals play a very important rôle in the first stage of adaptation to the conditions of the environment. After this first stage, however, the changes necessary for the acquisition of further adaptation take place in the peripheral tissues. In this stage, the stimulus ceases to be "alarming" and therefore the adrenal hormones are no longer required for the process of adaptation.

We assumed that the symptoms of the alarm reaction are mainly due to the liberation from the tissues of some toxic metabolite (possibly histamine or some physiologically similar compound). If this assumption should prove to be correct, one would have to conclude that the function of the adrenals is to detoxify this metabolite. In this event, there would be no contradiction between our interpretation of adrenal deficiency and the intoxication theory as such or possibly even its more modern modification, the histamine intoxication theory (Lucas). The circulatory theory (Swingle and co-workers) and the carbohydrate theory (Britton and Silvette) consider one symptom of the alarm reaction—the circulatory disturbance in the first case, and the hypoglycemia in the second case—to be the basic cause of all the deficiency symptoms. In the light of our findings, these seem to be the result rather than the cause of the deprivation syndrome. The cause of it is the decreased resistance to alarming stimuli. That is why all these deficiency symptoms will appear in adrenalectomized animals at a time when they would otherwise not be evident—that is, immediately following exposure to an alarming stimulus. It seems quite likely that the loss of sodium which is the basic change according to those who believe in the sodium deficiency theory (Loeb, *et al.*) or the increase in potassium (Zwemer) or the deficiency in phosphorylation (Verzar) or the increase in non-protein nitrogen—all of which have been considered to be the primary change—are also symptoms rather than the cause of adrenal insufficiency.

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THE SYNTHESIS OF SUBSTANCES RELATED TO LYSERGIC ACID

A VERY probable structure for lysergic acid (formula I), the characteristic constituent of the ergot alkaloids, has been derived from the interpretation of, among other things, its characteristic groupings and degradation products.[1] Recently attempts have been made to substantiate this formulation by synthesis. As a first step we have checked the possibility of the production of that portion of this structure composed of the 3-ring system, 3,4-trimethylene indole (formula II). A method to accomplish this was found in the reduction of naphthostyril (the lactam of 8-amino-1-naphthoic acid) with sodium in butyl alcohol. As a by-product a substance normally to be expected was simultaneously formed, *viz.*, 1-hydroxymethyl-8-amino-1,2,3,4-tetrahydronaphthalene. The identities of these substances were shown by their production by a different procedure, namely, reduction of the methyl ester of 8-amino-1,2,3,4-tetrahydro-1-naphthoic acid.

Trimethylene indole exhibits the usual indole reactions but not, however, the characteristic Keller reaction given by the ergot alkaloids (lysergic acid). A nearer approach to the synthesis of lysergic acid

[1] W. A. Jacobs and L. C. Craig, *Jour. Biol. Chem.*, 115: 227, 1936.