

PROCEEDINGS

COMMUNICATIONS

GESELLSCHAFTSVERHANDLUNGEN

DANISH SOCIETY OF ALLERGOLOGY

Meeting on November 25th, 1960.

ANTIBODIES TO INTRINSIC FACTOR

by MICHAEL SCHWARTZ, Copenhagen.

So far the nature of intrinsic factors remains obscure; such factors, however, are generally admitted to contain a protein—a mucoprotein—and they are known also to develop in the fundus ventriculi of man. The intestinal resorption of B¹² occurs when the extrinsic and intrinsic factors have fused. This process is rather slow as compared e.g. to the intestinal resorption of glucose.

Patients with pernicious anaemia have atrophic gastric mucosa, not infrequently also atrophic gastritis. In such cases orally administered B¹² will be excreted with the faeces. If active intrinsic factor preparations be added to the B¹² vitamine a resorption will occur even in patients with pernicious anaemia. With a view to identifying the B¹² it should be labelled with radioactive Cobalt (⁵⁸Co or ⁶⁰Co).

Schilling's test: oral administration of 0.5 microgramme of radioactive B¹² followed, 2 hours later, by intramuscular injections of 1000 microgrammes of non-radioactive B¹², which will be absorbed instantaneously and the concentration in the blood will rise steeply. A certain amount of B¹², not linked with protein, will now be present in the plasma and hence, will be excreted in the urine. Also in healthy subjects a certain amount (10-40 %) of the labelled, oral B¹² will be present in the urine. No radioactive B¹² is found in urine from patients with pernicious anaemia.

For the last nine years pernicious anaemia has been treated by oral administration of preparations containing small amounts (50 mg) of pyloromucosa from pigs and 5 microgrammes of B¹² combined in one tablet. At first the response to the drug will be quite satisfactory but if treatment be continued for 6-12 months some patients will present

falling haemoglobin and erythrocyte values even if the dose be increased. Eventually the haemoglobin percentage will be at the same low level as it was when treatment was instituted. Injections of the drug at this stage will increase values again to normal levels. *But* now the oral administration will have lost its effect never to be resumed except occasionally and several years hence, if ever. This condition is termed a „blockade“ of the patient.

The question arises whether such resistance to the oral preparation may be ascribable to a development of antibodies or to some acquired immunity. Indeed, it must be remembered that taking of these tablets also involves an introduction of an alien protein (pylorus of pigs).

Examinations of the condition “blockade” disclosed the following features:

Oral administration of B^{12} + 100 mg of pyloromucosa from pigs:
no absorption.

Oral administration of B^{12} + 800 mg (or more) of pyloromucosa from pigs:
satisfactory absorption.

Oral administration of B^{12} + gastric juice from *rats*:
satisfactory absorption

Oral administration of B^{12} + human intrinsic factor:
satisfactory absorption.

Absorption of orally administered B^{12} + gastric mucosa from wild boars was found, in previous experiments, to be satisfactory in patients with pernicious anaemia which remained untreated; this preparation was *not* absorbed in patients in whom a blockade had developed.

The experiments suggest the presence of a specific antibody. The phenomenon of blockade may be ascribable to an immunity in connection with a heterologous intrinsic factor, e.g. a local intestinal immunity. Resorption of B^{12} , however, may be satisfactory even in cases of blockade provided that large amounts (3500 mg) of pyloromucosa from pigs be administered simultaneously. Such massive doses will presumably “overwhelm” the intestinal canal.

Initial treatment for 5 days by prednisolon failed to change the low B^{12} absorption in three cases of blockade. Such initial treatment must probably cover periods of several months if an increased absorption is to be resumed.

No blocking effects were involved in the "obsolete" anti-pernicious anaemia preparations. Modern preparations, however, in which the ratio of B^{12} to intrinsic factor is high involve such blocking effects. It has been suggested to make preparations less efficient by increasing the ratio of B^{12} dose to dose of intrinsic factor, but a blockade was found to develop more rapidly after these drugs.

A number of cases of blockade have been found to resume the capability of absorption of B^{12} if only the oral administration of the intrinsic factor be discontinued. Even at best it will take several months before the capability of absorption is regained. Total blockade may recur by the introduction of oral administration of pyloromucosa from pigs for a couple of weeks (amnesic reaction). The localization of the antibody remains obscure but the site may be the intestinal mucosa.

In the search for the blocking antibody a circulating antibody was found. This is illustrated as follows.

In an untreated case of pernicious anaemia Shilling's test demonstrated a slight absorption of B^{12} . Normal absorption was demonstrated in the same patient after administration of B^{12} + intrinsic factor + serum containing intrinsic factor antibody, the B^{12} absorption will be insignificant, but it will rise to normal levels after administrations of B^{12} + intrinsic factor + normal serum.

The antibody is not specific and consequently it cannot explain the phenomenon of blockade. The antibody is present in the globulin fraction of serum protein. It disappears from the blood after daily administration for a couple of months of 80 mg of hydrocortisone. These details suggest that the antibody is a true one. The mechanism of the antibody remains to be elucidated. The intrinsic factor is known to convey B^{12} through the intestinal mucosa and it is also known that *all* intrinsic factors will bind B^{12} . The effects of the intrinsic-factor-antibody might be explained as follows:

- I. it may prevent linkage between the intrinsic factor and B^{12} but experiments have shown that this is not the case.
- II. the antibody may prevent the B^{12} + intrinsic factor complex from gaining a foothold in the intestinal mucosa and this theory seems more probable.

Blood from 39 normal subjects was examined but no antibody was found which might inhibit the B^{12} absorption. Antibody against intrinsic factor was demonstrated in 25 per cent in blood from patients with untreated pernicious anaemia. Most probably, pernicious anaemia may

be an auto-immune disorder in which the antibody against intrinsic factor develops initially. Cells in the stomach, producing the factor may be eliminated by the antibody upon which—when depots in the liver of antianaemic nature are exhausted—a pernicious anaemia will develop.

Two antibodies are known to be present in pernicious anaemia:

- (1) an acquired antibody developed by oral administrations of tablets containing B¹² + intrinsic factor. This antibody is specific and probably localized to the intestinal mucosa.
- (2) a circulating, spontaneously developed antibody, possibly of an auto-immune nature, and considered to be an immunity antibody. It is *not* specific.

The most favourable modern treatment of pernicious anaemia includes injections of B¹². However, such treatment is not of a “physiological” nature since the intrinsic factor is absent in these patients.

This document is a scanned copy of a printed document. No warranty is given about the accuracy of the copy. Users should refer to the original published version of the material.