Tilting into the head-down position did not alter the systolic pressure during the first 12 days of life.

We thank Dr. J. Forest Smith and Mr. A. J. Wrigley for allowing us to make these observations on their cases; Sisters Gale and Harris and the midwives for their kind help and co-operation; Professor Henry Barcroft for facilities; and Dr. A. C. Dornhorst for valuable comments.

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INTRINSIC FACTOR AND VITAMIN B₁₂ ABSORPTION*

BY

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With the isolation of vitamin B₁₂ (cyanocobalamin) it soon became obvious that Castle's original hypothesis was erroneous and that intrinsic factor did not react with an extrinsic factor to form haematinic principle which was stored in the liver. The more simple concept was formed that intrinsic factor was concerned with the absorption of vitamin B₁₂ from the intestine. This led to much intensification of work connected with its isolation and possible clinical application.

Glass, Boyd, Rubinstein, and Svigals (1952) demonstrated that it was associated with a more or less crude mucoprotein fraction of the gastric juice, and they therefore suggested that it might also be mucoprotein in nature. In my own laboratory, work was carried out on the preparative paper strip electrophoresis of human gastric juice (Latner, Ungley, Cox, McEvoy-Bowe, and Raine, 1953). A substance with intrinsic factor activity was present on the anode section of the paper strip. It contained hexosamine and was therefore probably mucoprotein in nature. This led to further chemical procedures and the eventual preparation of highly potent material.

The first work which we carried out was concerned with precipitation at low pH and subsequently with alcohol at low temperatures (Latner, Merrills, and Raine, 1954). We soon realized that this could possibly lead to breakdown of biological material, and we therefore decided to attempt isolation of the factor by the use of ion-exchange resins. This led to the production of a highly potent product which had a molecular weight of approximately 15,000 (Latner, Merrills, and Raine, 1956). The material was homogeneous on electrophoresis at two different pH values, as well as in the ultracentrifuge. Its activity, both clinically and by the radioactive vitamin-B₁₂-absorption test, was higher than any material previously described. There was little doubt that the material was a mucoprotein.

Williams, Ellenbogen, and Esposito (1954) have prepared a substance of molecular weight 5,000 which also had high intrinsic factor activity. Since they used trypsinization in their isolation procedure it was not unlikely that they might have broken down a substance of higher molecular weight. An important point, however, was the fact that both their material and our own possessed very low vitamin-B₁₂-binding power.

Holdsworth (1957) has claimed to have isolated a substance of molecular weight 40,000 which has vitamin-B₁₂-binding power and which is highly active as intrinsic factor.

It seems that three substances with intrinsic factor activity have been prepared from pig gastric mucosa—a mucopolypeptide with a molecular weight of 5,000, and two mucoproteins, one with a molecular weight of approximately 15,000 and another with molecular weight of 40,000. This has led to some confusion. If one considers Holdsworth's material as a possible precursor of intrinsic factor produced by the gastric mucosa and that modification of this precursor both in the stomach and in the small intestine eventually leads to intrinsic factor of relatively low molecular weight, then the whole position is more or less clarified. In relation to this concept it is interesting to note that O'Brien, Taylor, Turnbull, and Witts (1955) have prepared from human gastric mucosa a substance with intrinsic factor activity which has a molecular weight of about 40,000. Its activity in human beings was much less than the pig material we ourselves have isolated. It seems, therefore, that the material in question should really be regarded as a precursor of intrinsic factor.

Absorption Tests

In order to try to shed some light on this rather confusing picture, we have for some time been undertaking isolation procedures with freeze-dried pig pyloric mucosa. After treatment by ion-exchange and precipitation procedures this has yielded a preparation which has proved remarkably potent on clinical trial (see Fig.). There is no doubt that the clinical response was completely maximal. We gave 5 mg. of our intrinsic factor preparation daily together with 5 µg. of vitamin B₁₂. We have therefore carried out intestinal absorption tests at this dosage, and we have been able to demonstrate that we were able to bring about an absorption of approximately 2 µg. daily.

It is interesting that the ion-exchange procedures have also led to the isolation of material which has proved to be inhibitory to vitamin-B₁₂ absorption (Latner and Merrills, 1957). This material is mucoprotein in nature, possesses a molecular weight approximately equal to that of the intrinsic factor mucoprotein, but has a different tyrosine: tryptophan ratio. The behaviour on electrophoresis is remarkably like that of the intrinsic factor. The existence of such a substance is of the highest significance. Recent work throwing possible doubt on the efficacy of prolonged oral treatment in pernicious anaemia (Schwartz, Lous, and Meulengracht, 1957) should not be regarded as the final word in this matter. It is obviously still necessary to test preparations which are known not to contain inhibitor. Especially is this the case since the inhibitory effect in rats is still present some weeks after a single dose of inhibitor has been taken (Latner, unpublished observations).

We will now consider the physiological mechanisms concerned with the absorption of vitamin B₁₂ and the

*A lecture delivered to the Section of Pathology of the Manchester Medical Society, in the University of Manchester, on March 12, 1958.

Results of treatment with 10 daily consecutive doses of an intrinsic-factor preparation and vitamin B₁₂ compared with a control period with vitamin B₁₂ alone.

part played by intrinsic factor. A good deal of experimental work in this field has recently been carried out on rats. This is because their absorption mechanism has proved to be similar to that in human beings (Clayton, Latner, and Schofield, 1955; Watson and Florey, 1955).

Control of Intrinsic Factor Production

Nervous.—A number of normal human beings apparently absorb very little vitamin B₁₂ under the conditions of the usual radioactive vitamin-B₁₂-absorption tests. If these individuals are given an injection of carbachol (0.25 mg.) at the same time as they are given their radioactive vitamin B₁₂ there is an increase in absorption (Baker and Mollin, 1955). This would appear to indicate that parasympathetic stimulation increases the production of intrinsic factor, since carbachol has no effect on absorption in patients with pernicious anaemia.

Endocrine.—Bacon Chow (1956) has shown that after hypophysectomy in rats there is markedly diminished absorption of vitamin B₁₂. This is due to diminished production of T.S.H. Thyroidectomized animals behave in a similar fashion. We have shown that antithyroid drugs inhibit the absorption of the vitamin in the rat (Clayton and Latner, unpublished observations). It would seem, therefore, that the endocrine system plays some part in the absorption mechanism, but that the details of this action are still to be worked out. The effect might be on production of intrinsic factor or directly on the intestine itself.

Site of Absorption of Vitamin B₁₂

Evidence is accumulating with regard to the actual site of absorption of vitamin B₁₂. Our own work with the rat has indicated that most of the absorption occurs in the middle third of the small intestine (Latner and Raine, 1957a). This has been confirmed (Booth, Chanarin, Anderson, and Mollin, 1957). It is interesting that the vitamin is first of

all taken up by the intestinal wall and not released from this situation for approximately one hour. Cooke, Cox, Meynell, and Gaddie (1957) have come to the conclusion that in human beings absorption occurs mainly in the lower ileum. This has been deduced from studies of vitamin-B₁₂ absorption in patients with ileitis.

Mechanism of Absorption of Vitamin B₁₂

Some light is at last being shed on the possible mechanism of absorption of vitamin B₁₂. There is some controversy on whether or not binding of the vitamin by intrinsic factor is important in this respect. This, of course, arises from the fact that our own and Williams's intrinsic factor preparations bind very little vitamin B₁₂ but are very potent, whereas other preparations have definite vitamin-B₁₂-binding power. Much work has recently been published which indicates that binding of the vitamin is important. It is, however, a matter of some significance to point out that, although binding has been demonstrated to be of some consequence, it is not necessarily binding to intrinsic factor itself, but may well be to another constituent of the concentrate under investigation. It would be difficult, however, to adopt this point of view in the case of a vitamin-B₁₂/intrinsic-factor complex (Holdsworth, 1957) which appears homogeneous by various physical methods of examination. However, it is possible that even in this material we really have intrinsic factor forming a complex with another protein which itself has high binding power for the vitamin.

Using the urinary excretion test of absorption of the vitamin, Schilling and Schloesser (1957) performed some interesting experiments which demonstrate the importance of binding. Normal human gastric juice was incubated with radioactive vitamin B₁₂ and then the normal vitamin was added. Another sample of the juice was incubated with ordinary vitamin B₁₂ and then the radioactive vitamin added. In this way two portions of gastric juice were prepared which contained equal total quantities of the vitamin, but one sample possessed the radioactive vitamin in the bound form and the second the non-radioactive vitamin in this state. Each sample in turn was fed to patients. Evidence was gained from the excretion of radioactivity in the urine that there was preferential absorption in the bound form. Similar observations have recently been made in Castle's laboratory using gastrectomized rats as experimental animals (Nieweg, Shen, and Castle, 1957).

A number of workers have shown that pig intrinsic factor concentrates inhibit absorption of vitamin B₁₂ in the intestine of the intact rat. Similar findings with some intrinsic factor preparations have been observed in healthy human beings, but other preparations increase absorption (Williams, Chow, Ellenbogen, and Okuda, 1957). It has been suggested that this inhibition phenomenon may be some form of species specificity of intrinsic factor, but it now seems likely that it is due to the presence of some inhibitory substance. Possibly vitamin-B₁₂ binding by inhibitory substances renders the vitamin unavailable to the animal in question. This idea is further supported by the fact that human gastric juice in doses of 0.5 ml. inhibits absorption in the rat, but much smaller doses increase absorption (Latner, unpublished observations).

Wijmenga (1957) has presented what I consider to be the most likely hypothesis in relation to the mechanism of vitamin-B₁₂ absorption. He has suggested that this might take place in two stages. First, a special type of binding to some protein or proteins, and, secondly, the absorption of this bound form across the intestine under the influence of intrinsic factor.

Schilling and Schloesser (1957) have demonstrated that the binding of vitamin B₁₂ by human gastric juice is highly specific with most samples. They have shown that adding large quantities of pseudovitamin B₁₂ to gastric juice has no effect on the final binding power of the gastric juice for the vitamin B₁₂. They have also shown that administration of large amounts of pseudovitamin B₁₂ has no effect on the

absorption of vitamin B₁₂ itself in the human intestine, and so there is no form of competition for absorption between these two substances. They therefore suggest that a highly specific form of binding is important from the point of view of absorption and consider that this binding is to intrinsic factor itself, since the intrinsic factor preparation they used showed the same binding specificity. I would like to suggest that experiments of this type do not preclude a specific system in the gastric juice for binding vitamin B₁₂ to some protein, in accordance with Wijmenga's suggested first stage. Eventually this specifically bound form is absorbed in the intestine under the action of intrinsic factor. Such a protein system could well have been present in the intrinsic factor preparation that Schilling employed. As I have already pointed out, our own material does not bind much vitamin B₁₂. We have evidence that to some extent this binding is inhibited by pseudovitamin B₁₂.

In my own laboratory, absorption has also been studied in the intact rat (Latner and Raine, 1957b). We have shown that pseudovitamin B₁₂ does not compete for absorption with vitamin B₁₂, a finding which confirms the work of Schilling in the human. On the other hand, in our experiments with isolated rat intestine (Latner and Raine, 1958) we have demonstrated that there are two systems for vitamin-B₁₂ uptake, one of which is competitive with pseudovitamin B₁₂ and the other highly specific. It thus appears that the specific binding system of the intestine is concerned with the actual absorption of the vitamin, since this is unaffected by the pseudovitamin.

We have extended our vitamin-B₁₂ uptake studies to liver slices (Latner and Raine, 1957c). Here we have demonstrated that the uptake is highly specific and is non-competitive with pseudovitamin B₁₂. The recent interesting observation (Miller, Raney, and Hunter, 1957) that intrinsic factor increases the uptake of the vitamin by liver slices has been confirmed. We have shown that this increased uptake is prevented by the addition of pseudovitamin B₁₂. It would thus seem at first sight that the increased uptake is part of a competitive system. We have, however, also determined by ultrafiltration the amount of vitamin B₁₂ that is bound by the intrinsic factor preparation we used under various experimental conditions and shown that the liver uptake is in actual fact proportional to the amount of vitamin bound by the preparation. Pseudovitamin B₁₂ inhibits the increased uptake because it inhibits binding. We are hoping that liver slices may be more simple to study than isolated intestine, since in isolated intestine there may well be some rat intrinsic factor which has been absorbed before the animal was killed. It is not impossible, therefore, that studies of liver slices which have not previously been in contact with intrinsic factor may possibly shed some light on the mechanism whereby the vitamin is absorbed into cells and possibly across the intestine. This is not too improbable a suggestion, since we must remember that embryologically the liver is formed by a budding-off process from the foregut.

We are also accumulating evidence that the absorption mechanism would appear to be enzymatic. In the first place, by giving increasing doses of radioactive vitamin B₁₂ to the intact rat we have obtained an absorption curve of a type corresponding to the well-known Michaelis and Menton equation of enzyme activity in relation to substrate concentration (Clayton, Latner, and Schofield, 1957). Secondly, our vitamin-B₁₂ analogue studies have demonstrated that the intestinal absorption is highly specific and is prevented by interchanging the desdimethyl moiety of vitamin B₁₂ for adenine as in pseudovitamin B₁₂, or by altering one of the side chains on ring B of the vitamin (Latner and Raine, 1957a). This is a type of chemical specificity which is all too familiar in known enzyme mechanisms.

Action of Sorbitol

Recently it has been shown that sorbitol, a hexahydric alcohol derived from glucose, will increase the absorption of

vitamin B₁₂ from the intestine (Greenberg *et al.*, 1957). This arose from observations that the preparation "liptril" increased the absorption of vitamin B₁₂ in healthy young and old people (Chow, Horonick, and Okuda, 1956). It has now been demonstrated that the component responsible for this effect is sorbitol. We have confirmed that this compound increases vitamin-B₁₂ absorption from the intestine of the normal rat (Latner and Raine, unpublished observations). This, however, happens only when the dose of the vitamin, as well as that of the sorbitol, is very high and definitely outside physiological levels. The mechanisms involved are probably related to simple diffusion.

After sorbitol administration at high-dosage level there is great distension of the intestines, and we feel that this also plays some part in the increased absorption. It is highly debatable, therefore, whether the sorbitol effect is going to shed any direct light on the action of intrinsic factor itself, although it is a tempting notion that the carbohydrate moiety of intrinsic factor mucoprotein might be responsible for the absorption of vitamin B₁₂. Among various other substances tested (Greenberg *et al.*, 1957) it has been shown that D-mannitol, L-sorbitol, and D-xylose also have the ability to enhance vitamin-B₁₂ absorption.

Clinical Application

Diagnostic

The use of radioactive vitamin B₁₂ in the study of intestinal absorption of the vitamin has naturally led to diagnostic applications. Absorption tests are of great value in patients who have been given vitamin B₁₂ in spite of the fact that the diagnosis of pernicious anaemia was not definitely established before therapy was instituted. Help is also obtained in the differential diagnosis of subacute combined degeneration (Berlyne, Liversedge, and Emery, 1957). Studies are made before and after administration of an intrinsic factor preparation by mouth, and it is demonstrated that the intrinsic factor restores absorption to normal. Some normal people have a relatively low absorption, which can be increased by the administration of carbachol (Baker and Mollin, 1955), but no such increase occurs in patients with pernicious anaemia or subacute combined degeneration. The intestinal absorption of vitamin B₁₂ is often defective in steatorrhoea, but in this instance intrinsic factor preparations produce no improvement.

The actual techniques of determining absorption involve giving a known dose of radioactive vitamin B₁₂ by mouth and determining the amount that appears in the faeces (Heinle, Welch, Scharf, Meacham, and Prusoff, 1952; Calender, Turnbull, and Wakisaka, 1954) or in the urine (Schilling, 1953). In the latter instance it is necessary to give a massive flushing dose of ordinary vitamin B₁₂ intramuscularly about an hour after the radioactive vitamin has been administered orally.

Other techniques have been elaborated which do not require the collection of either urine or faeces. They are the determination of intestinal absorption by measurement of radioactivity over the liver some days after administration of the test dose (Glass, Boyd, Gellin, and Stephanson, 1954), and, more recently, the study of the radioactivity of the blood, which rises to a maximum in normal individuals some eight hours after oral administration but does not rise in patients with pernicious anaemia unless an intrinsic-factor preparation is also given (Booth and Mollin, 1957).

Therapeutic

As has already been mentioned, it is still possible that intrinsic-factor preparations not containing inhibitor substances will play some part in the treatment of pernicious anaemia. Recent observations relating to diminished activity after prolonged administration must be repeated with non-inhibitory intrinsic-factor preparations before prolonged oral therapy is said to be contraindicated in pernicious anaemia. Unfortunately, insufficient material of this nature has so far been prepared for clinical trial.

It is now recognized, as a result of absorption studies, that there is defective vitamin-B₁₂ absorption after total gastrectomy and in many instances after partial gastrectomy. It is therefore important that the vitamin should be administered intramuscularly to certain patients after these operations have been performed. Similar remarks apply to patients with ulcerative colitis and certain types of ileitis.

In view of the fact that large oral doses of vitamin B₁₂ lead to appropriate absorption in the absence of intrinsic factor it is probably sufficient to administer massive dosage of the vitamin by mouth. This could apply to the treatment of pernicious anaemia, but remains to be proved by prolonged clinical trials. In any case, it is important to realize that patients who have developed megaloblastic anaemia as a result of defective absorption will have severe depletion of their vitamin-B₁₂ stores. It is impossible to restore this to normal by intestinal absorption alone, and it is therefore important, in the first place, to give vitamin B₁₂ in relatively large doses intramuscularly.

Summary

There are now at least three highly purified preparations of intrinsic factor, with molecular weights of approximately 5,000, 15,000, and 40,000 respectively. They are apparently homogeneous and belong to the group of mucoproteins. The two with lower molecular weights have low vitamin-B₁₂-binding activity.

A substance has also been obtained which inhibits vitamin-B₁₂ absorption. The presence of such a substance or substances in intrinsic factor concentrates could explain certain inhibitory phenomena previously ascribed to species specificity. This has been borne out by the observation that human gastric juice in small quantities stimulates absorption of vitamin B₁₂ in the rat but is inhibitory in larger amounts. The last word has not yet been said in relation to the clinical use of intrinsic factor preparations by mouth, since a single dose of the inhibitory substance maintains its effect on vitamin-B₁₂ absorption for a long period.

Intrinsic-factor secretion is under the influence of the parasympathetic nervous system and possibly also the thyroid.

The intestinal absorption of vitamin B₁₂ has been shown to occur in the middle third of the small intestine in the rat but possibly in the lower ileum in human beings.

It seems that some form of binding to protein is necessary for intestinal absorption of vitamin B₁₂. This binding need not be to intrinsic factor itself. Studies of absorption with increasing dosage, as well as with analogues of the vitamin, present evidence that an enzyme mechanism is involved in its intestinal absorption.

It has recently been shown that sorbitol, a hexahydric alcohol derived from glucose, increases the absorption of vitamin B₁₂ from the intestine.

New knowledge in relation to intrinsic factor and vitamin B₁₂ has proved of use both in diagnosis and in therapy, especially in relation to treated pernicious anaemia, subacute combined degeneration, gastric resections, and intestinal disorders.

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WEBER-CHRISTIAN DISEASE WITH VISCERAL INVOLVEMENT AN EXAMPLE WITH HEPATIC ENLARGEMENT

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Although commonly known in English-speaking countries as Weber-Christian disease, a typical example of the syndrome was first published by Pfeifer (1892), and details of a second patient were described by Gilchrist and Ketron (1916). It was Brill (1936) who first referred to the condition as Weber-Christian disease, and on the Continent it is commonly known as Pfeifer-Weber-Christian disease. Weber (1925) drew attention to these two previously recorded patients in his own paper, and there is no doubt that to him must go the credit of recognizing the condition as a distinct entity. To Weber's original title "Relapsing Non-Suppurative Nodular Panniculitis" Christian (1928) added the word "febrile" to emphasize an important feature likely to arouse the interest of the clinician.

The object of recording this case in some detail is to emphasize that the disease has been too long considered as localized to the skin, whereas certain viscera and other organs may be extensively involved by the fatty metamorphosis. Such involvement may give rise to varied symptoms, including retrosternal pain, pain and swelling in joints, pain in bone, and also abdominal pain, and these symptoms may prove puzzling if the syndrome is not recognized. Rarely the visceral involvement is so extensive that it results in death.