graft-versus-host disease,[14] and infection by intestinal parasites.[15] We have suggested that the presence of a local C.M.I. reaction may be the common factor which produces partial or sub-total villous atrophy in many clinical and experimental conditions—e.g., cow's milk allergy, cœliac disease, giardiasis, and acute gastroenteritis.[6,15] However, although mucosal infiltration with lymphoid cells is a constant feature in these conditions, there is no information as to whether, in man, normal or diseased small-bowel lymphocytes are T cells, B cells, or some other cell type. Many tests of lymphocyte nature and function involve lymphocyte-culture systems, and it has now been shown that jejunal mucosal biopsies, including their populations of lymphocytes, can be maintained in organ culture for two to three days.[16] Thus, it seems reasonable to apply to cultured intestinal mucosa techniques similar to those which have been used in the investigation of functions of blood-lymphocytes.

In this preliminary work we have used the secretion of an M.I.F. by cultured fragments of intestine in the presence of α-gliadin as an index of C.M.I. We found no evidence of M.I.F. secretion when biopsy specimens from several groups of patients were cultured in the absence of added antigen. The addition of α-gliadin to the culture system did not result in M.I.F. secretion by non-cœliac mucosa or by the mucosa from two patients with cœliac disease treated with a gluten-free diet. Furthermore, the addition of α-gliadin to the culture-medium after the organ culture but before the M.I.F. measurement did not inhibit migration in the 7 patients so tested. However, when biopsy specimens of small-intestinal mucosa from patients with untreated cœliac disease were cultured with α-gliadin, they secreted a factor into the culture-medium which inhibited the migration of normal human leucocytes. Falchuk et al. have also demonstrated secretion of a humoral factor by cultures of jejunum from patients with cœliac disease in the presence of gluten fraction III, but they attributed this activity to IgA antigluten antibodies complexed with gluten or with the enterocyte cell surface.[17] Immune complexes have M.I.F. activity in some circumstances,[18] but it seems unlikely that the critical antigen/antibody ratio which is required for the production of toxic immune complexes would be obtained in all of our cultures of cœliac mucosa with gliadin. We believe that it is more likely that the M.I.F. which we detected is a lymphokine—i.e., a mediator of cellular immunity secreted by sensitised lymphocytes in the presence of antigen (gliadin). Other possible explanations of our findings may be that the effete enterocytes extruded from the cultured mucosa have a non-specific inhibitory effect on cell migration or that the lymphocytes in the intestinal mucosa spontaneously secrete an M.I.F. However, both of these explanations seem unlikely since under such circumstances M.I.F. activity would have been secreted by the cœliac mucosa whether or not α-gliadin was present in the medium.

There have been abnormally large numbers of intra-epithelial lymphocytes in the small-intestinal mucosa of virtually all cœliac patients so far studied.[4–6,19,20] Animal models of delayed hypersensitivity produce partial or sub-total villous atrophy with crypt hyperplasia.[6,12–14,21] These findings have pointed to the possibility that a local C.M.I. reaction may be present in cœliac disease, and the results of our in-vitro studies of jejunal-biopsy specimens further support this theory. It is likely that within the intestinal mucosa in cœliac disease there are both humoral and C.M.I. reactions to gliadin (and perhaps to other antigens). Our work on local hypersensitivity in animal models indicates that it is probably the delayed hypersensitivity component of a local immune response which causes villous atrophy and crypt hyperplasia in the small-intestinal mucosa.[6,21,22]

This work was supported by grants from the National Fund for Research into Crippling Diseases, the William Gibson Research Scholarship of the Royal Society of Medicine, and research facilities supplied by E. Merck Ltd. The purified α-gliadin was prepared and supplied by Dr D. Evans of the Department of Histopathology, Royal Postgraduate Medical School, London.

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Hypothesis

PROSTAGLANDINS AND OBESITY

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Summary In metabolic obesity energy in triglyceride stores is not readily accessible, and lipolysis to free fatty acid and glycerol seems to be somehow restrained. In the normal situation, there is a balance between a forward reaction via cyclic A.M.P. ending in lipolysis and a negative-feedback mechanism in which prostaglandins participate. In metabolic obesity there may be a biochemical error leading to overproduction of prostaglandins; as a result the forward reaction is overwhelmed and lipolysis does not take place. Since

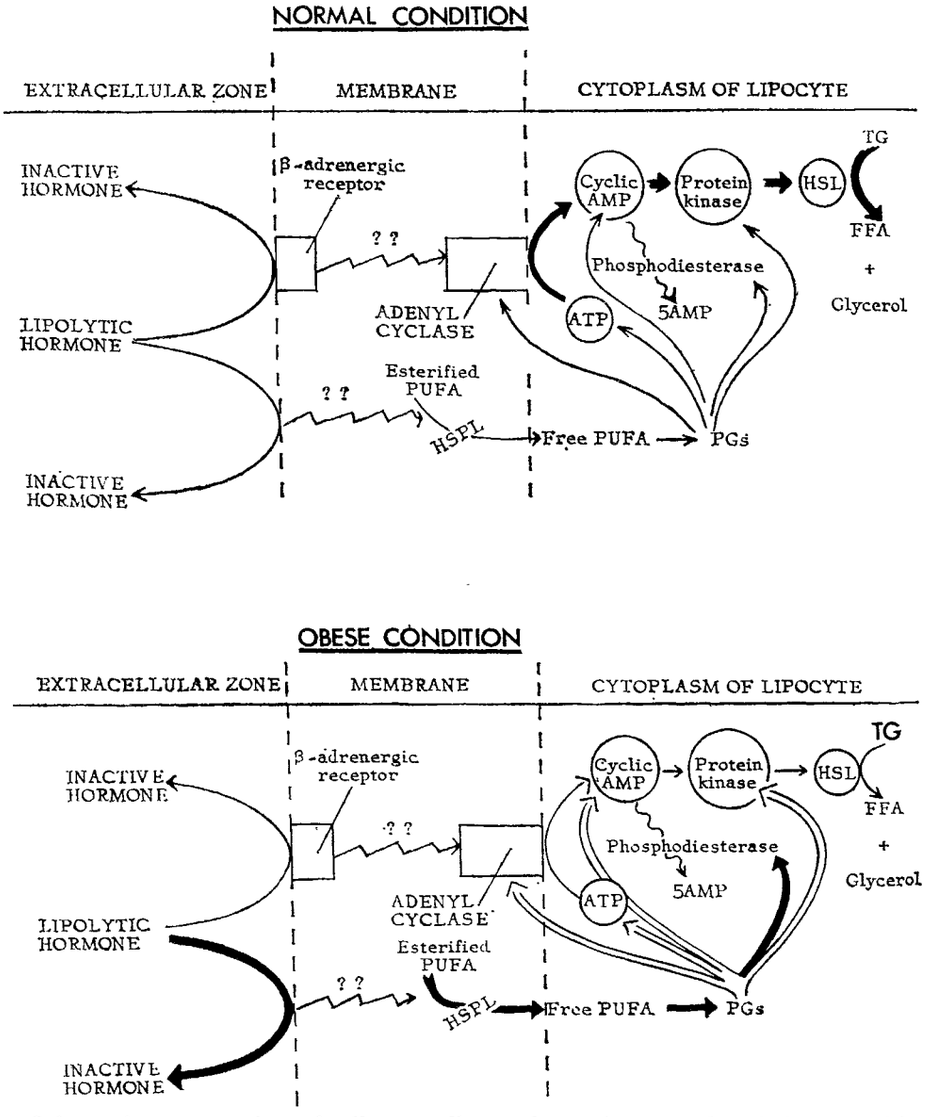
prostaglandin antagonists and inhibitors of prostaglandin synthesis are known, this hypothesis is not without therapeutic interest.

IN obesity the body contains an excess of depot fat triglyceride (T.G.).[1] The heterogeneity of the condition[2] indicates a multifactorial ætiology and probably explains why treatment has had varying success. The many forms of animal obesity[3] have been divided into two groups—regulatory and metabolic.[4] Whereas regulatory obesity includes that resulting from experimental manipulation (e.g., chemical[5] or surgical[6,7] destruction of ventromedial nuclei), metabolic obesity is the result of an inborn error of metabolism, as in the yellow obese mouse, OBOB mouse, NZO mouse, Zucker rat,[8] and genetically fat pig,[4,10] and as proposed in the human situation by Astwood.[11] This form of metabolic obesity has now been described in man as triglyceride-storage disease.[12] In this situation, adipose tissue failed in vitro to respond normally to isoprenaline and to release free fatty acids (F.F.A.) and glycerol. Thus, although the tissues had abundant reserve calories in the form of stored T.G., these stores were relatively unavailable for the production of energy since they could not be readily mobilised for use in the general metabolic pool. Thus, in situations of metabolic stress when F.F.A. normally represents the body's major source of calories, such supplies are severely restricted in metabolic obesity.

Shaw and Ramwell[14] showed that prostaglandins E_1, E_2, and $F_{2\alpha}$ were released from adipose tissues incubated in vitro during stimulation by the lipolytic agonists adrenaline, noradrenaline, and adrenocorticotrophic hormone (A.C.T.H.), and that there was a decrease in prostaglandin release from adipose tissue in the presence of insulin. Prostaglandins may antagonise fat-cell lipolysis, and this antagonism can be overcome by prostaglandin antagonists such as the low-molecular-weight fraction of polyphloretin phosphate (P.P.P.),[15] 7-oxaprostaglandins,[16] or prostaglandin-synthetase inhibitors like indomethacin.[16] Indeed, adipose tissue from Zucker obese rats which was insensitive to the lipolytic action of noradrenaline and A.C.T.H. in vitro readily released glycerol in the presence of P.P.P. (unpublished).

Endogenous prostaglandins have been implicated in a negative-feedback mechanism by which they modify lipolysis in adipose tissue.[13–16] Two components have been suggested for the lipolytic stimulus (see figure): (1) adrenergic receptor stimulation/adenyl-cyclase excitation leading, by means of cyclic A.M.P. and protein kinase, to hormone-sensitive lipase activity with concomitant glycerol and F.F.A. production, and (2) hormone-sensitive phospholipase action to release polyunsaturated fatty acids esterified in the fat-cell membrane and subsequent synthesis of prostaglandin to act as a physiological, negative-feedback inhibition or "switch-off" control mechanism, which blocks hormone-sensitive lipase activity.

Prostaglandins may manifest their action at a variety of intracellular sites: at a specific prostaglandin receptor site in the cell membrane,[17] by inhibition of adenyl-cyclase activity,[18,19] by interaction with A.T.P.ase,[20] so regulating A.T.P. availability for conversion to cyclic A.M.P., or by interference in the activities of cyclic-A.M.P., phosphodiesterase,[21] protein kinase,[16,18] hormone-sensitive lipase (unpublished), hormone-sensitive phospholipase, and prostaglandin



Schematic presentation of adipose cell membrane in normal and obese condition.

In the normal condition the two stimuli provoked by a lipolytic hormone (e.g., noradrenaline) are cyclic A.M.P. formation (resulting in lipolysis) and a balanced prostaglandin production. The lipolytic hormone becomes inactive not because of any change in its molecular configuration but because it ceases to manifest an effect. In obesity, prostaglandin production is excessive, and this results in reduced physiological response (i.e., lipolysis) due to inhibition at one or more steps (e.g., A.T.P. availability, adenyl-cyclase action, cyclic-A.M.P. binding to protein kinase, protein-kinase actions, or enhancement of phosphodiesterase activity).

HSL=hormone-sensitive lipase; TG=storage triglyceride; FFA=free fatty acids; PUFA=polyunsaturated fatty acids (especially arachidonic); HSPL=hormone-sensitive phospholipase; PGs=prostaglandins (especially E).

synthetase.[22] Thus, the switch-off mechanism in adipose cells may be acting at any one (or more) of these sites. It is the delicately regulated balance of the forward reaction (resulting in F.F.A. production) and the inhibition reaction (prostaglandin antagonism of the cyclic A.M.P. system, at one or more sites) which enables the normal utilisation of calories stored in adipose tissue. If this balance is disturbed, a pathological state ensues. I suggest that metabolic obesity results from such a disturbed balance by a biochemical lesion manifested during lipolytic stimulation by an overproduction of prostaglandins. This result is the second facet of the lipolytic response (prostaglandin negative-feedback inhibition) overwhelming the cyclic A.M.P. forward reaction. Thus fat mobilisation is switched-off almost before it has begun, and little (or no) F.F.A. or glycerol is released. The result is that the adipose tissue operates a sink mechanism: whatever is put in becomes irretrievable. Thus, adipose mass gradually increases. Dietary glucose and liver and muscle glycogen are the other major sources of readily available body fuel; their rapid depletions may help to explain the apparent lethargy of the obese. Obesity might, then, be treated by administration of a prostaglandin antagonist or synthetase inhibitor, designed to be adipose-tissue specific. When these therapeutic agents are applied and the P.G. block removed, there will be lipid released into the circulation in increasing quantities. This increase should be taken gently in order that it does not itself produce more problems—e.g., hyperlipidæmia. In-vivo studies have shown that indomethacin will reduce the body-weight of normal rats (unpublished) and of genetically obese Zucker rats and their lean litter-mates (unpublished); yet other observations (ref. 23 and unpublished) are compatible with a regulatory role for prostaglandins in fasting lipolysis. It is of relevance, too, that in rheumatoid arthritis patients undergoing regular aspirin therapy there was a conspicuous reduction (compared with the normal population) in the frequency of mortality due to accident, hypertensive heart-disease, and myocardial infarction.[24] Since these conditions are associated with overweight,[25] it is logical to assume that there was an abnormally low incidence of overweight patients in this aspirin-treated population.

Prostaglandins may also be important in the development of obesity by an effect on lipogenesis. Prostaglandin E_1 has been shown to be insulin-like in enhancing re-esterification and de-novo synthesis of fat in adipose tissue.[26,27] Further, P.P.P. antagonises both basal and insulin-stimulated U-^{14}C-glucose uptake by fat cells (ref. 15 and unpublished). Whether or not P.P.P. manifests its antilipogenic (anti-insulin) action by antagonism of endogenous prostaglandins, or by inhibition of Na^+-dependent glucose transport[28] (notwithstanding the possibility that these processes may not be mutually exclusive), remains to be elucidated. A role for prostaglandins in the general action of insulin on cells must remain conjectural for the present.

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Reviews of Books

Aldosterone and Aldosteronism

E. J. Ross, University College Hospital Medical School, London. London: Lloyd-Luke. 1975. Pp. 501. £8.

WITH many monographs the reader is often left confused, bewildered, and dismayed at a profusion of conflicting observations and ideas; he may rightly suspect that the author is as unable to draw a coherent synthesis of the scene as the reader is to see it. Thus the monograph becomes an exhaustive repository for names, titles, and references. Professor Ross's book on aldosterone is a notable exception: his balanced, thoughtful, and very readable work leaves the reader not only richer in knowledge, but wiser in understanding. His discussion of the chemical, physiological, and clinical aspects of his subject is directed with great skill and presented with admirable clarity. Most of the important facts about aldosterone in health and disease are now well-established, but that is not to say that Professor Ross offers a catalogue to a mausoleum. Far from it; many aspects are incompletely understood, such as the mechanism of action of the hormone, its action on extrarenal tissues, the relationship between aldosterone-induced renal sodium retention and potassium loss, and the mechanism of renal escape. As he sifts and stirs the evidence, the author constantly qualifies the results, stressing the concentration of hormone used and weighing up the differences in experimental design. He is as interesting when exploring gaps in understanding as he is in bringing together what is known, especially in his discussion of the evidence for an aldosterone-stimulating hormone. Such faults as there are are small: aldosterone concentrations are confusingly given in a mixture of units; borrowed tables are not always adequately explained; and too rigid a separation may have been made between the clinical significance of adrenal adenomas, microadenomas, and nodular hyperplasia (indeed the histopathology deserves more explanation and qualification). Professor Ross has continued to be active in aldosterone research without losing a balanced view—minutely know-

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