mine conjugated insulin (rhodamine-lactalbumin-insulin) used for these studies retains < 2% of the activity of native insulin [7]. It is therefore difficult to see how one can arrive at physiologically significant conclusions from these experiments. Furthermore, the fluorescence is visualized using image intensification microscopy, and the clustering observed could be an order of magnitude greater than the micro-aggregation seen by electron microscopy. Hence the data obtained with rhodamine-insulin might not be comparable to that of Fm-I, and molecular models of receptor aggregation [1] may not be applicably to these fluorescence studies.

Jeffrey [1] also cites the work of Kahn et al. [8] to support the tenet of insulin-induced receptor aggregation. Monovalent Fab' fragments of anti-receptor antibody were shown to bind to the insulin receptor but were unable to stimulate glucose oxidation. Addition of anti-Fab' fragments restored the ability of the Fab' fragments to stimulate glucose oxidation. Kahn et al. concluded [8] that anti-receptor antibody acts by aggregating the insulin receptor. However, their data may have alternative interpretations. For instance, once can postulate that there are separate binding and biological response sites for the insulin receptor, with corresponding complementary sites for the insulin molecule and the anti-receptor antibody. When the anti-receptor antibody is split into its Fab' fragments, a minor conformational change might occur, resulting in the retention of binding activity, but loss of the ability to stimulate biochemical activity. The addition of anti-Fab' antibody can perhaps expose the sites for biological activity on the Fab' fragments by restoring the original conformation. There is then no need to invoke receptor aggregation to explain the biochemical activity of the anti-receptor antibody or insulin.

Any hypothesis concering the role of groups of insulin receptors must account for all the pertinent morphological and biochemical observations including the following. First the natural state of distribution of insulin receptors appears to be tissue specific [2, 4, 9]. Secondly dithiothreitol, a reducing agent, disperses the groups of Fm-I occupied receptors on adipocyte membranes [10], yet increases ^{125}I-insulin binding to these membranes about threefold [11]. Thirdly anti-insulin antibody [5] induces aggregation of the largely single Fm-I occupied receptors on liver membranes, and causes up to a 15-fold increase in ^{125}I-insulin binding to liver membranes [12].

In conclusion, the validity of the interpretations from experimental data [6, 8] used to support the concept of insulin-induced receptor aggregation, can be questioned. There are experimental findings to endorse the opposite view that insulin does not aggregate its own receptor [2, 4, 5]. Receptor aggregation, nevertheless, does occur in the natural state of certain tissues [2, 9] and may not be necessary as a primary mechanism for insulin action. However, there might be a secondary role for receptor aggregation in modulating the biochemical responses to insulin [5, 11, 12]. Studies are needed to determine whether the pattern of aggregation of the insulin receptor seen in the natural state is an intrinsic property of the receptor structure or the membrane micro-environment for each individual tissue.

Yours sincerely,
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Antiplatelet / Anticoagulant Drug Therapy in Severely Uncontrolled Diabetes Mellitus

Dear Sir,

We wish to comment on the Letter to the Editor by Janka and Mehnert [1] on the role of antiplatelet agents in diabetic ketoacidosis. There have recently been several reports of haemostatic changes in diabetic coma [2, 3] and, while a coagulopathy may exist, its association with fatal thromboembolic events has not been established. In the hope of decreasing mortality from fatal thromboembolism and, in turn, lowering overall mortality from uncontrolled diabetes (up to 50% in the elderly [4]) some investigators have proposed prophylactic anticoagulation in these patients [5–8]. This has gained increased support in the literature and while antiplatelet drugs are not recommended, it has been suggested that heparin may be warranted in high risk uncontrolled diabetic patients. In a recent review of 275 cases of uncontrolled diabetes (unpublished observations), we noted one cerebrovascular accident in a hyperosmolar patient as well as one mesenteric arterial occlusion and one cerebrovascular accident in ketoacidotic patients. In reviewing several large series and case reports including 251 cases of hyperosmolar coma and 1,764 cases of ketoacidosis, we found that major fatal or near fatal thromboembolic (pulmonary embolus, cerebravascular occlusion, mesenteric arterial occlusion or limb loss due to arterial occlusion) represented less than 1% of events in ketoacidosis and 6% in hyperosmolar coma (references available on request). Many of these events occurred with severe hypotension and might just as easily be explained by increased serum viscosity with low flow in an already compromised circulation rather

than by any 'coagulopathy'. A number of large series dating back earlier than the 1950's were deliberately excluded from this review since they do not distinguish between vascular occlusive events and an infectious aetiology for terms such as 'gangrene' and thus are uninterpretable with respect to the anticoagulation issue.

Fatal thromboembolism may not be as common as suggested in the literature. However, gastrointestinal bleeding (usually mild) is a well known and frequent occurrence in uncontrolled diabetes [9]. If anticoagulation is used in these patients as part of routine resuscitation, we could see an increase in serious gastrointestinal haemorrhage. Until prospective studies demonstrate the value and safety of heparin in lowering mortality in these patients, we oppose its routine use unless overt thromboembolic disease exists. Earlier referral for treatment and prompt, aggressive volume repletion may also serve to reduce these complications while we await prospective investigations.

Yours sincerely,
P. Carroll and R. Matz

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Book Reviews

G. P. Kozak. Clinical Diabetes Mellitus. Philadelphia London Toronto: W. B. Saunders 1982. pp 541, hardback US $ 55.00. ISBN: 0-7216-5502-5

This volume achieves its objective as stated in the Preface, of being a general review of diabetes for the non-specialist, although lactic acidosis and insulin allergy and resistance receive rather too much attention for such a general review. However, this well produced and attractively presented book contains excellent general reviews on the aetiology and metabolic derangements of diabetes; a simple survey of ketosis management and an excellent attempt to cover all the major problems of caring for the adolescent diabetic, stressing that so many of these are not to do with the metabolic problem. For the practising clinician, detailed and attractive presentations to do with foot care, chiropody and the neuroarthropathic problems of the diabetic cannot be bettered. The chapter on diet seems rather too long and surprisingly no mention is made of the increasing enthusiasm and benefits of the high fibre diet. In the Appendix there are a number of useful diet sheets and examples of meals, along with other very useful information contained in that part of the book. Colour plates of the retina and skin lesions are a useful addition. Physicians on the European side of the Atlantic could be irritated by the support given to the use of large bolus injections of insulin in ketosis, the general lack of enthusiasm for home blood glucose monitoring and the use of long-acting insulins in surgical treatment of diabetes. The chapter on autonomic neuropathy comments on cardiorespiratory problems of such patients, although in the section on anaesthesia no mention is made of this practical danger.

Such minor criticisms are more to justify the place of the reviewer than to underrate this excellent volume, which should prove valuable on medical units and indeed on practising diabetic units. I recommend it very warmly. J. D. Ward (Sheffield, UK)

A. K. Khachadurian, S. H. Schneider: Diabetes and Metabolic Diseases. Modern Directions in Therapy. New York: Medical Examination Publishing 1982. pp 157, hardback US $ 24.75. ISBN: 0-87488-679-1

This is a well written short book which is informative and easy to read and clearly reflects the authors' practical experience in the care of the metabolic disorders discussed. However, it is not a comprehensive text being restricted in the main to diabetes mellitus, obesity and hyperlipidaemias. There are technical difficulties for European readers in that most of the biochemical values, diets and ideal weight ranges are given with the US physician in mind. Personally I find this self-imposed isolation of US publications (particularly in the metabolic field) regrettable.

It is difficult to be sure for whom this book is intended but would seem to be most useful to physicians who are not engaged in the full-time care of patients with metabolic diseases (and perhaps some who are). I would recommend this text for the informative and valuable practical advice it gives to the young physician at the outset of his career. J. K. Wales (Leeds, UK)