LIVER

STUART J SAUNDERS & JOHN TERBLANCHE

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Proceedings of an International Liver Conference with special reference to Africa held at the University of Cape Town Medical School

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Editors' Foreword

This volume contains the proceedings of the International Liver Conference with special reference to Africa held at the University of Cape Town Medical School from January 22nd to January 26th, 1973. The Conference was held under the auspices of the South African Medical Research Council, the Cape Provincial Administration and the University of Cape Town.

Our special thanks go to Mr E S Vorster and Miss C M Hayward of the Public Relations Department of the SAMRC for the outstanding manner in which they both worked to make the Conference a great success. We are grateful to the members of the Organizing Committee for all their help and for the subediting of some of the discussion periods published here. We are indebted to many others, both on the University and Medical Research Council staff for generously giving of their time, both in the planning of, and during, the Conference.

We are particularly grateful to the many speakers who travelled from afar, gave of their knowledge and made the Conference a truly international one.

We are indebted to Dr Roger Williams for his thoughtfulness which greatly eased our task as editors.

Finally, we would like to thank Mrs Betty Dickens of Pitman Medical for her advice and help, charmingly and expertly given over a distance of 6000 miles.

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This International Liver Conference was held under the auspices of the South African Medical Research Council, the University of Cape Town and the Cape Provincial Administration and was arranged by the Public Relations Department of the MRC.

Hierdie Internasionale Lewerkonferensie was deur die Suid-Afrikaanse Mediese Navorsingsraad, die Universiteit van Kaapstad en die Kaapse Provinsiale Administrasie aangebied en was deur die Skakelafdeling van die MNR gereël.

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The Natural History of Australia Antigen

B S BLUMBERG
USA

INTRODUCTION

Since our discovery of Australia antigen (Au) (Blumberg et al, 1965) and its relation to hepatitis (Blumberg et al, 1967) much of the work in this field has been focused on this disease. In this paper the relation of Au to human biology (particularly genetics and maternal effects) and to the cause (or causes) of cancer will be emphasized. Au is, in some situations, associated with leukaemia, hepatoma and possibly other cancers, and further knowledge of the nature of Au may help us to understand the nature of agents which may cause these and other cancers.

In the earliest papers on Au we suggested that it might be a virus. In 1965 (Blumberg et al, 1965) we said, "... the Australia antigen is related to the virus which has been suggested as the cause of leukaemia," and the following year (Blumberg et al, 1966) (in reference to hepatitis) "... a virus or other infective agent could lead to the presence of Australia antigen, perhaps due to a direct effect on the genome."

When we reported the association with hepatitis, we immediately set about testing the hypothesis that Au was the virus which causes 'viral hepatitis', and during the next four years accumulated a body of evidence, which for the most part supported this view (Blumberg et al, 1973a). There were, however, some features of Au which were not typical of a virus although none of these actually ruled out the hypothesis. At the same time we continued to test the notion stimulated by our earlier work on the lipoprotein 'Ag' system (Allison & Blumberg, 1961) that Au had the properties of an inherited serum constituent, a protein polymorphism. None of the accumulated data has ruled out this hypothesis either. On first consideration it might appear that these two hypotheses are mutually exclusive, but there is, in fact, no reason to assume that this is so. Therefore, since neither of the hypotheses had been ruled out they were combined to give a third hypothesis (definition) which is, in effect, a restatement of the properties of the agent. Australia antigen is associated with an infectious agent which causes

some types of hepatitis in man and has the properties of a serum protein polymorphism.

An extension of this view states that there are additional agents, related to other diseases, which have properties similar to Au. In order to designate this group of agents we have suggested the term 'Icron', an acronym on the name of The Institute for Cancer Research. The statement of this hypothesis does not imply that the preceding ones are ruled out; a considerable amount of energy and effort is still being spent testing the virus hypothesis. For example, it is possible that Au is not the infectious agent causing hepatitis, but that there is another causative agent (perhaps an extremely small one) which has not yet been discovered but which has many of the properties of Au. However, testing the 'Icron' hypothesis has the advantage of encouraging studies of characteristics not included within the rubric of a conventional virus.

THE NATURE OF AUSTRALIA ANTIGEN

On the basis of studies, initially from our laboratory and subsequently others, a picture is beginning to emerge of the nature of Australia antigen. Some of these features are consistent with the definition of a virus, others appear to be atypical, but none rule out the possibility that Au acts as an infectious agent causing (some) hepatitis in man. In this section, we will attempt to summarize these results in the form of a general description of the properties of the agent.

Infectious agents are always associated with the disease they cause, although the reverse is not necessarily true, ie infectious agents may be associated with diseases they do not cause, and in addition the agent may be found in apparently normal individuals who do not have the disease (or diseases) caused by the agent. Au is found in higher frequency in patients with acute viral hepatitis (both 'infectious' and 'serum') and in some forms of chronic hepatitis. It is also found in the blood of many individuals who are not apparently ill and who appear to be asymptomatic carriers. The frequency of carriers varies from very low values (about 0.1% in North American and North European communities) up to about 20% in some Oceanic, Asian and tropical communities. In this respect its distribution is similar to that of a serum protein polymorphism whose frequency may vary from population to population, presumably depending on local ecological and selective factors. There is a striking difference in host reaction to 'infection' with Au, which has been discussed in detail elsewhere (Blumberg et al, 1970a). The same agent which has had no noticeable effect on some individuals, the carriers, will cause acute, chronic, and sometimes fatal illness in others. One man's meat is another's poison: 'normal flora' in a carrier is a pathogen in another person. This dichotomy between carriers and affected individuals holds true for many, conceivably most, infectious agents.

AUSTRALIA AFFINITY GROUP

Au is also associated with a group of other diseases, that is, it occurs in higher frequency in these diseases than in controls. These diseases, termed the 'Australia affinity' group are characterized by impairments in their immune mechanism. They include the lymphocytic leukaemias, Down's syndrome, lepromatous leprosy (as opposed to tuberculoid leprosy) chronic renal disease and hepatoma.

In some of these (for example, Down's syndrome) the presence of Au is accompanied, in general, by chronic anicteric hepatitis. It is possible that Au is related to the aetiology of some of these diseases (ie, hepatoma). Another possibility is that individuals who are susceptible to persistent infections with the agents responsible for these illnesses are also susceptible to persistent infection with Au; that is, these agents have an affinity to each other in that they have an affinity to a common susceptibility factor. (This susceptibility factor may be inherited - see below.) If this is true they may also have other features in common and, as a consequence, knowledge about Au may help to identify and understand the mode of action of other agents related to the 'Australia affinity' diseases.

For example, there is an increased frequency of Au in patients with lymphocytic leukaemia who have received transfusions of donor blood, some of which contains Au. The frequency is higher in the transfused leukaemia patients than in other patients not in the 'Australia affinity group' who have also received transfusions, because the leukaemia patients, when exposed, are more likely to develop a persistent infection with Au. The agent responsible for lymphocytic leukaemia may have other characteristics of Au, and these characteristics can be used as a basis for formulating hypotheses about leukaemia and its aetiologic agent, ie, the sex distribution of lymphocytic leukaemia is similar to that of Au ($M > F$); family distribution is similar, age distribution similar, etc and these hypotheses can be tested. The same predictions relating to sex, age, genetics, maternal effect, which have been formulated from the experience with Au, can also be made for hepatoma and certain other members of the affinity group (Blumberg et al, 1973a).

Several years ago we isolated Au and examined it under the electron microscope (Bayer et al, 1968), and this has now been done by many investigators. Its appearance is compatible with that of a small virus; it is 200 Å in diameter and has fine structure detail. Larger units (400 Å) may also be seen, but whether these are antigenically related to Au is still unclear. An unusual feature, in respect of the viral hypothesis, is that there is doubt as to the existence of nucleic acid in these particles. Joswiak et al (1971) using a starch block method for isolation, reported that Au contained about 5% RNA. This was subsequently confirmed by Millman et al (1973), but he was unable