WORLD HEALTH ORGANIZATION

INTERNATIONAL AGENCY FOR RESEARCH ON CANCER

LIVER CANCER

Proceedings of a Working Conference held at the Chester Beatty Research Institute, London, England, 30 June to 3 July 1969

IARC SCIENTIFIC PUBLICATIONS No. 1

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The Agency conducts a programme of research concentrating particularly on the epidemiology of cancer and the study of potential carcinogens in the human environment. Its field studies are supplemented by biological and chemical research carried out in the Agency's laboratories in Lyon and, through collaborative research agreements, in national research institutions in many countries. The Agency also conducts a programme for the education and training of personnel for cancer research.

The publications of the Agency are intended to contribute to the dissemination of authoritative information on different aspects of cancer research.

The authors alone are responsible for the views expressed in the signed articles in this publication.

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FOREWORD

In 1956, a seminar on cancer of the liver—organized by the Geographical Pathology Committee of the International Union against Cancer (UICC)—was held in Kampala, Uganda, under the chairmanship of Dr Harold Stewart.[1] *The objective of this seminar was to review the available data on the disease and to recommend lines for further study. Scientists from many parts of the world gathered at the seminar, which stimulated increased interest and work on what is one of the most frequent types of cancer in certain countries.*

Clinical and experimental interest in liver cancer has grown since 1956. Additional information on the biology of human liver cancer has become available from Africa and Asia, while on the experimental side many new chemical hepatocarcinogens—including certain naturally occurring mycotoxins—have been discovered and studied in the laboratory. In the latter context, the rat liver has also proved most valuable in biochemical studies on the carcinogenic process. Furthermore, the production of hepatomas in mice and rats by a chemical is often used as an index of that chemical's potential carcinogenic activity in man.

Disappointingly, in spite of these developments, there has until recently been a strange lack of co-ordination between animal and human investigations. Laboratory experiments have often been designed with little reference to the situation in man, and the results obtained have consequently been scarcely relevant to the human problem. Conversely, relatively little effort has been made to study the application to man of some of the more exciting findings in the laboratory.

Some ten years after the Kampala seminar, the International Agency for Research on Cancer (IARC) came into being. Established within the framework of the World Health Organization, but empowered to develop its own research programmes, IARC is concerned with promoting international collaboration in all aspects of cancer research.

By 1958, it had become clear that it would be valuable to provide a forum where workers concerned with liver cancer in the laboratory, in the clinic and in the field could meet and discuss problems of mutual interest. It was hoped that such a combined multidisciplinary approach might prove successful in unravelling the etiology of liver cancer, which has not only been observed to present wide geographical variations in incidence but has also been the subject of extensive experimental investigations. If the problem of liver cancer etiology could not thus be solved, there would be little hope for enlightenment regarding the etiology of neoplasms of other sites, where less adequate information was available.

The proposal to convene a symposium was first put forward by workers at the Chester Beatty Research Institute, London, and since the suggestion happened to coincide with an expansion of IARC's activities on liver cancer, it was felt that it would be mutually

[1] *Acta Un. int. Cancr.*, 1957, **13**, 516-873.

advantageous for the two groups to join forces. Accordingly, a working conference, with Professor Sheila Sherlock as chairman, was held at the Chester Beatty Research Institute from 30 June to 3 July 1969.

Before the conference authoritative reviews were circulated to provide bases for the discussions, which were aimed at assessing the state of knowledge in the field and estimating the priorities for future research. The participants hoped that in the discussions they had not only clarified their own thinking, but had also re-emphasized some of the fundamental difficulties associated with solving the problem of liver cancer in man. The discussions themselves were not recorded, but each of the three subcommittees that were set up during the conference submitted a report on its work.

The papers prepared for the conference, together with summaries of the reports and recommendations of the subcommittees, are presented in this publication. Wherever possible, the papers have been revised to include references to work that had not been completed at the time of the conference.

In conclusion, I should like to thank all those—and especially the authors of the reviews published here—who participated in this attempt to bring together the existing knowledge from the clinical and experimental fields.

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PAPERS PRESENTED

Pathogenesis and Morbid Anatomy of Human Primary Liver Cancer

PETER J. SCHEUER [1]

This paper is devoted mainly to the pathology and pathogenesis of liver-cell carcinoma, the commonest of the primary malignant tumours of the liver. This carcinoma has not always been distinguished clearly from other neoplasms—notably, carcinoma of the intrahepatic biliary tree—and some published series have analysed the two types of tumour together. Therefore, the paper also deals briefly with tumours other than liver-cell carcinomas, since the distinction is important in any consideration of associated diseases and pathogenesis.

Berman (1951), in his monograph on primary carcinoma of the liver, has discussed earlier classifications and nomenclature. A clear separation of carcinomas into two groups stems from the early part of the present century. Many different names have been used to designate the two tumours, from which Berman chooses hepatocellular carcinoma, for a tumour assumed to arise from parenchymal liver cells, and cholangiocellular carcinoma, for one thought to arise from the intrahepatic bile ducts. Edmondson & Steiner (1954) prefer to use liver-cell carcinoma and bile-duct carcinoma, a terminology that avoids possible confusion, since the term "cholangiocellular" could also be taken to refer to tumours falling into the liver-cell group but differentiating into ducts or gland-like structures rather than liver-cell plates. In the uncommon mixed liver-cell and bile-duct tumours there is sometimes doubt as to whether the bile-duct element implies a separate tumour or merely varied differentiation in the same tumour. Beswick & Scott (1958) conclude that true mixed tumours are probably rare, and Edmondson (1958) and Gall (1960) consider that they should be regarded as variants of liver-cell carcinoma. Other names used for mixed tumours include combined carcinoma, mixed carcinoma, hepatobiliary carcinoma and cholangiohepatoma.

Table 1 lists some of the synonyms of the principal two forms of liver carcinoma. A full classification of liver tumours, including embryonal and connective tissue neoplasms, is given by Edmondson (1958).

TABLE 1

SYNONYMS OF PRIMARY CARCINOMAS WITHIN THE LIVER

Liver-cell carcinoma	Bile-duct carcinoma
Carcinoma of liver	Carcinoma of bile ducts
Malignant hepatoma	Malignant cholangioma
Hepatocellular carcinoma	Cholangiocellular carcinoma
Trabecular carcinoma	Cholangiocarcinoma

LIVER-CELL TUMOURS OF CHILDHOOD

Before discussing the commoner adult carcinoma, it is necessary to consider tumours of the liver in childhood. The majority of these are either hepatoblastomas or liver-cell carcinomas. The hepatoblastomas, which may be purely epithelial or contain neoplastic mesenchymal elements, are embryonal tumours occurring almost entirely in infancy. The epithelial element is composed for the most part of embryonal liver cells or somewhat better differentiated foetal liver cells (Ishak & Glunz, 1967). Misugi et al. (1967) have found that under the electron microscope the liver cells in hepatoblastoma have few organelles and are thus unlike neoplastic or non-neoplastic parenchymal cells in adult liver. Hepatoblastomas appear to be entirely distinct from liver-cell carcinomas, which can also occur in

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