Festschrift to honour Professor Michael C Kew

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Chris Kassianides, Chairman of the Gastroenterology Foundation of South Africa, welcomed everyone and expressed thanks, on behalf of all the Trustees, to Professor Michael Kew, his wife Daphne and his son Garth who accompanied him from Cape Town. He introduced the Foundation by describing its origins as a Liver interest group over 20 years ago that he and Professor Pauline Hall, a hepatic pathologist at the University of Cape Town, had established. He paid tribute to Professor Mike Kew's contributions to Hepatology in South Africa and to the Foundation and, although the Foundation had its origins as a liver group, it has grown and developed over the last 10 years incorporating all aspects of Gastroenterology and Hepatology. Recognition and thanks was given to Jay Hoofnagle, Director of the Liver Disease Research Branch in the Division of Digestive Diseases and Nutrition at the NIH in Bethesda, MD, who hosted three of Mike Kew's fellows in his unit over a period of 20 years - Geoff Dusheiko, Adrian Di Bisceglie and Chris Kassianides.

Jay Hoofnagle began by reviewing Mike Kew's formidable career and body of world class research – more than 450 publications on various aspects of liver disease and viral hepatitis focusing on Hepatocellular Carcinoma (HCC) including all risk factors such as age, sex, smoking, alcohol, iron overload, aflatoxin, obesity and viral hepatitis. Not all his publications were confined to liver cancer and viral hepatitis; the liver in heat stroke, drug induced liver disease, renal disease, cirrhosis and amoebic liver abscess were publications on other aspects of liver diseases. The major focus, however, of his research was on the aetiology and molecular characteristics of HBV related HCC and the role of HBV mutations and replication. A landmark paper described the integration of HBV DNA into the genome of 12 patients with HCC published in the NEJM in 1981. He paid tribute to Mike Kew as an exacting investigator and academician. He concluded by congratulating Mike Kew on his rigorous questioning, generosity, his subtlety, his self-effacing nature and his enduring competitiveness. He remains, in Jay Hoofnagle's opinion, the consummate physician.

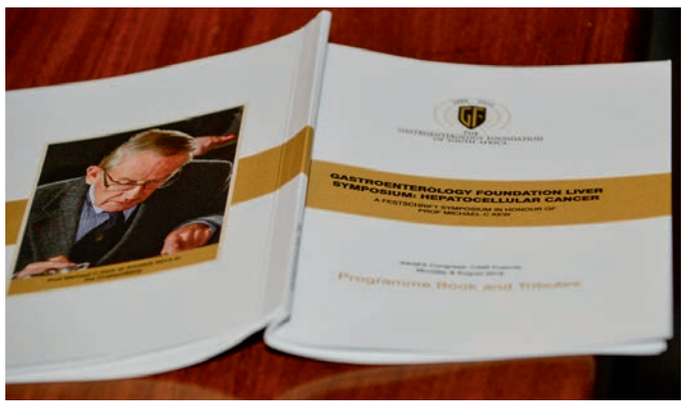
Prof Massimo Pinzani, Sheila Sherlock Chair of Hepatology and Director of the Institute for Liver and Digestive Health University College, London, reviewed Mike Kew's early years at the Royal Free with Sheila Sherlock. Mike Kew's research and work at the Royal Free Hospital on the hepato-renal syndrome formed the basis of his Phd thesis. This was in the swinging 60's, a time of great excitement in London. He began by giving an interesting account of the early years in the liver unit at the Royal Free Hospital and on the remarkable career of Dame Sheila Sherlock and "How British women became doctors" focusing on transforming the liver unit at the Royal Free into a truly international unit attracting fellows from all corners of the world. This included Mike Kew. Focusing on the hepato-renal syndrome he was the first to demonstrate in Gut in 1971 that the impairment of renal cortical blood flow was a consequence of portal hypertension. Further publications described the effect of Octapressin on renal blood flow in cirrhosis. A paper in the BMJ in 1971 co – authored with Dame Sheila Sherlock, was the first to review the Diagnosis of Primary Liver Cancer.

Professor Geoff Dusheiko, Emeritus Professor of Medicine, UCL Institute of Liver and Digestive Health, Kings College and Royal Free Hospital London, reviewed current and future attempts towards the eradication of HBsAg and particularly cccDNA. He began by describing the therapeutic goals in treating Hepatitis B – HBsAg clearance, control of viral replication and in so doing prevention of HCC, prevention of disease related mortality and prevention of decompensated cirrhosis. He began by reviewing the early use of recombinant Interferon in chronic HBV infection and the improved results with the nucleotide antagonist Tenofovir disoproxil and alafenamide and their use in HBeAg negative chronic HBV. Recent evidence for the use of Tenofivir in the third trimester of highly viremia pregnant mothers with chronic HBV markedly reduces perinatal transmission of HBV.

The primary aims of antiviral therapy of HBV have been achieved; HBV can be prevented by vaccination and in the last three decades Interferon and six nucleotide analogues have been successfully used. This has resulted in delay in the progression to cirrhosis and reduced need for transplantation. Although cure is seldom achieved, cessation of treatment is now possible. Newer targets to eradicate chronic HBV include RNA interference capsid inhibitors and cccDNA inhibitors such as GS - 9620 , an oral TLR – 7 agonist. Ultimately a state needs to be achieved where remission of chronic hepatitis B virus is achieved with improved long term survivals. He concluded by quoting Maya Angelou (1928 – 2014) "We had come so far from where we started and weren't nearly approaching where we had to be but we were on the road to becoming better".

Professor Adrian Di Bisceglie, Chair in Internal Medicine and Chief of the Liver Diseases Section, Saint Louis University, Missouri, began his presentation on HCC treatment and outcomes by contrasting the late presentation of HCC in Sub Saharan Africans with that of the small and suspicious lesion that presents in Westerners on imaging. The initial approach is based on the Barcelona Clinic Liver Cancer staging classification and depends on the size of the lesions (< 2cm) and the number of nodules (3). Resection is best for the single lesion < 2 cm with normal bilirubin and normal portal pressure. Liver transplantation is an option for those with early stage disease, with single or up to 3 nodules less than 3 cm in size, with associated disease and/or increased portal pressure. A variety of loco–regional ablative techniques are available for intermediate stage B multinodular disease and include thermal ablative therapies (RFA), chemical ablation (Percutaneous ethanol injection) and catheter based embolo-therapies (trans arterial chemoembolization with or without Doxorubicin and Radio-embolization). Sorafenib is used in advanced disease with a median survival of 46 weeks. Other promising chemotherapies include Tivantinib (a selective oral inhibitor of MET) as second line treatment and Regorafenib, an oral multi kinase inhibitor of tyrosine kinase. Most promising however, is an antagonist to PD – 1 Nivolumab (Opdivo), a

Mike Kew



fully human IgG4 anti–PD - 1 monoclonal Ab - presently in an ongoing phase 2 dose escalation study in previously treated advanced HCC with or without chronic viral hepatitis. He concluded that HCC continues to rise with HBV and HCV carriers and NAFLD emerging as an aetiology. Effective therapies are available if HCC is diagnosed early but prevention with HBV vaccine and early therapy with HBV antiviral therapy remains possible.

Professor Anna Kramvis, Research Professor and Director of the Hepatitis Virus Diversity Research Unit at the University of the Witwatersrand. Together with Prof MC Kew she directed the Molecular Hepatology Research Unit of the MRC Cancer Association and the University of the Witwatersrand. She discussed the phylogeography and clinical relevance of HBV Genotypes which included molecular characteristics of HBV in HCC, molecular and functional characterization of sub genotype A1, and HBV HIV co-infection in Africa. The strains of HBV in Africa differ functionally and in molecular characterizations than from those out of Africa. With a population of 1 billon Africa has 75 million HBV carriers. Genotype distribution in Africa consists predominantly of genotype A in the South East, genotype D in North Africa and genotype E in West Africa; this may influence clinical manifestations of disease. Regardless of genotype, HBV carriers from patients from HCC have a higher frequency of pre- S deletion mutants. In addition the mean age of patients with HCC infected with Genotype A is 6 years younger than non-genotype A. HBV carriers with sub genotype A1 have lower viral DNA, more liver damage and an earlier risk of HCC and is due to the molecular characteristics of sub genotype A1. In Africa 25% of HIV infected individuals have HBV co-infection and 15% of these co-infected carriers are HBsAg negative. HBsAg negative carriers have similar viral loads and ALT levels and HBV carriers from HIV infected individuals have pre-S deletion mutants similar to those HBV carriers from HCC patients. HBV HIC co-infection progresses to cirrhosis and HCC more rapidly and HBV co-infection negatively impacts on the natural history of HIV.

Professor Wendy Spearman, Head of the Division of Hepatology, Department of Medicine, University of Cape Town described efforts towards the total elimination of chronic HBV and HCC. Despite the availability of an effective vaccine since 1981 and effective antiviral therapy, Hepatitis B remains a significant global problem with 350 – 400 million people world- wide and with a life time risk of cirrhosis, liver failure and HCC of 15 – 40%. South Africa has an HBsAg sero prevalence of 6.7% with ranges of 3 – 25% and with the highest rates in HIV co - infected adults. HBV accounts for up to 50% of all cases of cirrhosis and HCC. The impact of HIV/HBV co–infection cannot be underestimated; HIV

increases mortality and promotes HBV replication with a higher rate of fibrosis progression and a younger occurrence of HCC. Yet it is a vaccine preventable disease with the WHO recommendation of HBV vaccine into the EPI in 1991. To date 184 countries world-wide and 45 in Africa have incorporated HBV vaccination into EPI and in 2009 HBV birth dose vaccine was recommended for all countries. However by 2014 only 50% countries reported offering birth dose vaccine. In Taiwan universal vaccination has reduced the HBsAg seroprevalence in children less than 15 years from 10% in 1984 to 0.3% in 2009 and with a 50% decrease in the annual incidence of HCC. Similar results are reported from other Asian counties such as Singapore, South Korea and China. South Africa introduced universal HBV vaccination in April 1995 and now offers a hexavalent vaccine with an 18 month booster to the 6, 10 and 14 week EPI schedule. However in South Africa there is no birth dose, no catch up program and no formal policy of HBSAg screening in mothers. HIV pregnant mothers with a prevalence of 40% in KZN have a HBSAg prevalence of 7% vs 4.8% in HIV negative mothers and HBV DNA levels are twice as high. This results in high prevalence of HBV infection in children despite HBV vaccination. Prevention of HBV mother to child transmission is a critical step towards the global eradication of HBV and the subsequent development of HCC. Tenofovir in the third trimester is recommended in high viraemic mothers. Vaccination should also be offered to all high risk groups. In addition antiviral therapy to HBV infected individuals have an impact on the development of cirrhosis and HCC and improves liver related and all cause mortality but has not eliminated the HCC risk. Ultimately a cure aimed at eradication of cccDNA is awaited.

Professor Mark Sonderup, Senior Specialist in the Department of Medicine and Division of Hepatology at the University of Cape Town and Groote Schuur Hospital, discussed how global elimination of HCV can be achieved. He began by pointing out that world -wide deaths from HBV and HCV in 2013 approximated those deaths from HIV and TB (approx 1.3 million). Emphasis was placed on the WHO goal of eliminating viral hepatitis as a public health threat by 2030 with a 30% reduction in new infections and a 10% reduction in deaths by 2020. Just 8 countries contribute to 50% of all infections. HCV cure has become a reality and treatment with DAA without Pegylated Interferon has made HCV elimination possible with simpler, safer and more effective treatment. In addition an HCV SVR has reduced the 5 year risk of HCC by 70%. The major stumbling block is access to effective DAA treatment. Targeting high risk groups in South Africa, such as IV drug abusers of which 70% are infected with HCV, sex workers and men who have sex with men screened for HIV, HBV and HCV is an initiative that began in July 2016, linking this program to care. If only advanced disease is treated HCV prevalence will remain over 30% in 2030. Combining treatment programs to include IV drug users and advanced disease for only 5 years not only reduces deaths but reduces the prevalence of HCV to less than 10%. Infected donor blood remains an important source of infection since 25 countries are not able to screen all donated blood for HIV, HBV or HCV. Countries that have successfully rolled out programs include Egypt, Iceland, Georgia, Australia and Rwanda. For non-cirrhotic patients 3 regimens are recommended Sofosbuvir with Ledispavir and Sofosbuvir with Daclatasvir for 12 weeks and Sofosbuvir with Ribavirin for 24 weeks. For cirrhotic patients Sofosbuvir with Ledipasvir for 24 weeks and Sofosbuvir with Daclatasvir for 24 weeks with or without Ribavirin for 12 weeks is recommended. Ultimately an effective vaccine is required. Access to care clearly needs to

Chris Kassianides, Sandie Thomson, Mike Kew with Bini in the background

be increased with awareness and discrimination.

Dr Mashiko Setshedi, Nuffield Post Doctoral Fellow at the University of Oxford, discussed the Molecular aspects of HCC that evolves through either a multi–step carcinogenesis that develops through progressive acquisition of genetic and epigenetic alterations or through a cancer stem cell concept where only a small subset of cells initiate and maintain tumour growth through cancer stem cells. Molecular pathways of hepato carcinogenesis include genetic (p53 tumour suppressor), Wnt/beta-catenin /CTNNB1 epigenetic (DNA methylation, histone methylation, chromatin remodeling, microRNAs) aberrant signaling paths (Wnt/Beta-catenin, Tyrosine kinase, vascular endothelial factor, transforming growth factor JAK/SATAT and ubiquitin proteosome) and immune mechanisms (infiltration with Tregs, Switching to Th2 response and increased PDL1). Specific effects of HBV induced hepato carcinogenesis were discussed – most HBV induced HCC occurs in the context of cirrhosis. The HBV protein – HBV X protein core and pre - S S protein have oncogenic activity. Most HBV induced HCC show integration of HBV DNA into the host genome which leads to genomic instability resulting in deletions, breaks and re-arrangements - gene activation or the production of fusion proteins also contribute. Aflatoxin induced p53 mutations inhibit oncogene apoptosis and DNA damage checkpoints and lead to cell proliferation and aneuploidy. Ultimately HCC develops where the balance between activating and inactivating mutations of oncogenes and tumour suppressors is altered. HCC is complex, a heterogenous clinical histological molecular phenotype that may be proliferative with a progenitor or hepatocyte – like lineage with high AFP, HBV related poorly differentiated and with a poor survival OR

Chris Kassianides, Mike Kew, Adrian Di Bisceglie, Jay Hoofnagle, Geoff Dusheiko

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Professor Lewis Roberts, Professor in Gastroenterology Cancer Research and Consultant in the Division of GI Hepatology at the Mayo clinic and Director of Research at Mayo Medical School posed the question whether HCC differs in different part of the world. Liver cancer is the 6th most common cancer and 2nd most common cause of death from cancer globally. HBV accounts for 54% of cases and HCV 31% whereas other causes such as aflatoxin and alcohol account for 15% of cases. Just as the HBV and HCV prevalence rates vary substantially globally so does the HCC prevalence rate. One of the largest global repository of HCC lies in Africa and through an African network for GI and Liver diseases factors contributing to the aetiology and pathogenesis of HCC in Sub Saharan Africa were analysed. 1521 patients with HCC from 7 African countries were collected with Ghana and Nigeria contributing to 37% and 23% of cases and Malawi, Ivory coast, Sudan, Uganda and Tanzania contributing the rest. HBV is associated with an earlier age of onset, 42 years compared to HCV of 55 years. There was substantial variation in the age of onset of HBV related HCC by country with the youngest occurring in Malawi, 35 years of age, and the oldest in Sudan, 58 years of age, and with the peak age of HBV associated HCC onset of 35 - 40 years. The youngest mean age of diagnosis of HCC in SSA results in the largest years of potential loss of life. The median survival of SSA HCC patients is 3 months vs 11 months in Egypt. A detailed pathology review in an attempt to identify the most highly significant mutations is underway. Reducing the burden of HCC in Africa requires screening for major causes such as HBV, HCV, Alcohol and NASH, identifying individuals at risk of HCC, enrolment in a surveillance program, confirming the diagnosis and finally, established treatment programs. With almost no surveillance programmes in SSA the median survival of HCC is only 3 months.

Professor Jose Ramos, Head of HPB Surgery at the Wits University Donald Gordon Medical Centre compared liver transplantation and liver resection in HBV related HCC emphasizing that treatment options in HCC are determined not only by the underlying malignancy but also by the underlying liver disease. Hepatic function is determined by the presence of ascites, albumin, bilirubin and alkaline phosphatase. Cirrhosis is present in 85% of patients with HCC and 15% have a normal liver. Fatty liver is present in 40% and fibrosis is 60%. Staging is performed using Child Pugh scoring system, indocyanine green clearance test and histology. Liver transplantation addresses both the diseased liver and the malignancy – failure is due to recurrence of HCC and liver transplantation may not be available to many HCC patients. Surgical resection only addresses the tumour and is limited by the state of the liver and extent of malignancy and both options are only applicable to a limited number of patients. Liver transplantation for stage 1 and 2 HCC has a 5 year survival of 70% and a 5 year recurrence rate of 15%. Surgery is not an option for a majority of patients with HCC and is only appropriate in CTP A and some B patients and only applies to 20 – 40% of patients. Improved resection is possible by improving surgical techniques, by segmental resection and by combining resection and ablation increasing the proportion of resectable cases by Portal Vein Embolization (PVE) and Trans Arterial Chemo Embolization (TACE) and by improving diagnostic imaging. PVE before liver resection can improve resectability and improve disease free survival. Can anything be done about the underlying state of the liver? Cirrhosis cannot be reversed but HBV can be treated and antiviral therapy decreases recurrence of HBV related HCC after curative resection and improves overall survival. Post-operative adjuvant chemotherapy has no benefit after surgical resection. There is some data for adjuvant interferon. Post-operative Sorafenib has a phase 2 trial in progress. Antiviral therapy of HBV and BCV and salvage transplantation offer the best option. Ultimately it is possible to increase resection rates and outcomes with better patient selection by improved staging and conversion therapy.

Professor Jean Botha, Head of the Liver Transplant Program at the Wits Donald Gordon Medical Centre reviewed the early days of liver transplantation in Johannesburg. In the 1980's 16 patients underwent liver transplantation including 3 children - 2 with biliary atresia and 1 with HCC under the leadership of Professor Burt Myburgh. Post operative mortality was high and the procedure was abandoned. Liver transplantation was resurrected at the DGMC in 2004 with 4 liver transplants performed in that year. In 2015 just over 40 Liver transplants were performed with an adult 5 year survival rate of over 80%. Liver transplant for HCC re – establishes normal liver function and eliminates the risk of de novo tumours developing and markedly reduces recurrence rates. The ideal candidate is an early HCC within Milan criteria of a single tumour < 5 cm or 2 – 3 tumours the largest < 3 cm with a Child's B or C cirrhosis with low AFP and without extra hepatic disease. The majority are transplanted within 6 - 12 months with a 5 year survival of 75% and a recurrence free survival of 92%. This far exceeds the survival of liver resection of 20 – 25% at 10 years. Selection criteria however are felt to be too restrictive and are now expanding to include a single tumour of < 6.5cm and 2 – 3 tumours the largest < 4.5 cm with a total diameter of < 8 cm. This results in a 5 year survival of 75%. The majority however are diagnosed at an advanced stage and liver transplant for advanced disease can only be achieved with successful down staging using a combination of TACE and RFA. At USCF this is achieved in 70% of patients. Salvage liver transplantation following resection is an option in some patients and if the transplantation is successful the results are comparable. Liver transplanation for HCC has a better overall and disease free survival compared to liver resection.

Mark Sonderup, Lewis Roberts, Adrian Di Bisceglie, Jose Ramos, Geoff Dusheiko. Front: Anna Kramvis, Jay Hoofnagle, Chris Kassianides, Wendy Spearman, Massimo Pinzani

Chris Kassianides
Chairman : Gastroenterology Foundation of SA