Chapter 1

Introduction - background, aims and methods

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BACKGROUND

The diagnosis of liver diseases depends on the interpretation of the outcome of a number of examinations. Central in the diagnostic process is the interpretation of the liver histology. For most liver diseases this is the essential step in making a good diagnosis. Therefore clinicians and pathologists need to cooperate closely in order to understand each other's input in deciding about the true diagnosis.

In general, and certainly also in the histopathological evaluation of liver disorders, there tends to be a large variation in the interpretation of a given tissue by different pathologists. Samples from one case may produce up to six different diagnoses when evaluated by ten pathologists. Such large inter-observer variations do also exist for many other observations made during the diagnostic process. However, since the histopathological evaluation is critical for the diagnosis of liver diseases, this aspect is a corner stone of our attempt to set up a world standard for diagnostic criteria of liver diseases of companion animals.

The apparent lack of standard criteria for defining the diagnosis has had several serious consequences. Firstly, in every day's practice there must have been many cases in which the diagnosis made was not correct, so that clinicians have treated many dogs and cats with the wrong medication. Many veterinarians have the impression that liver diseases are difficult to treat, which is in fact not true for the vast majority of the diseases. A solid diagnosis may usually be followed by successful therapy, but may of course also make clear that there is no treatment possible. A solid diagnosis is therefore the basis for all logical and evidence based veterinary interventions.

Secondly, by reading the scientific literature it becomes clear that there are reports on a certain disease which cannot be compared with other publications on the same disease, simply because the criteria used had been different. It is not unusual that different diseases were reported under the same name. This may make it very hard to compare the results and conclusions of one publication with those of another. Such confusions reduce the potential progress of the level of veterinary medicine, because it takes much time and many studies

before the truth becomes apparent and generally accepted. Good comparability of different publications on a certain disease is not the only profit to be gained. The development of rationally validated treatments has been largely hampered by the lack of solid diagnostic criteria.

When reviewing the literature, there are only very few, if any medications of liver diseases which have been tested in double blind, placebo-controlled studies. Such studies are required for the decision about the best treatment regime of diseases, and to decide about the added value of newly developed treatments in the future. Given the case load of most specialised clinics, controlled studies of the therapeutic effect of drugs can only be performed in a reasonable time span by the cooperation of different centres in each study (multi-centre studies). It is now time to make progress in this direction, but it is only possible when different participating centres can use solid and undisputed diagnostic criteria. Thirdly, the confusion has even been larger due to the fact that certain diseases have become more than one name. There has been insufficient reference to the existing literature and lack of scientific discussion to prevent this confusing practice. In this respect, separations seem to have existed between the new and the old world. This standardization process has been performed by specialists from all over the world, so that if required, one world standard name could be proposed if different names existed for one disease.

EXAMINATION

Pathomorphlogical examination is important, but only part of the diagnostic process of liver diseases. One of the most important advances in the past decade has been the complete incorporation of ultrasonography in veterinary medicine. Certainly for the diagnostic process of liver diseases ultrasound examination has become an indispensable tool. The generally accepted parameters to evaluate by ultrasonography have been summarized in Chapter 3 in association with techniques for liver biopsy. For different vascular disorders of the liver, however, ultrasonographic evaluation has become the cornerstone of the diagnostic process. For these diseases a standardized protocol is being described in Chapter 4, which permits to find portosystemic shunts and other vascular changes with a large degree of certainty.

Haematological and biochemical examinations are an integral part of the diagnostic process for liver diseases. However, most of these examinations are not decisive to diagnose a liver disease, but serve only to differentiate liver disease from other diseases with similar symptoms and signs. As soon as the presence of a liver disease has been demonstrated (e.g. by elevated liver enzymes or bile acids in plasma, or clinical icterus) the role of blood examination to decide about the diagnosis is very weak for most liver diseases except of the vascular disorders. Therefore the reader will find little information about blood examinations which are not essential in the diagnostic process.

This book starts at the point where the presence of a liver disease is apparent by the finding of elevated plasma enzymes, bile acids, or the presence of icterus.

AIMS

The aims of this book and the underlying efforts are to describe worldwide accepted standards and criteria for the diagnosis of all known liver diseases of dogs and cats. Pathologists and clinicians find well-defined histological diagnostic criteria, and precise definitions of chronicity stages. The variations with which diseases may present are described and exemplified. In addition unified nomenclature is proposed if a disease had been given different names. Clearly descriptive names are being proposed. The needed combination of diagnostic methods and their relative roles is given in schedules and tables, so that the reader

will have an immediate review of the essentials of the diagnostic process. The reader will find all relevant technical details about the diagnostic procedures used by clinicians, pathologists, and ultrasonographists.

We have aimed at giving relevant pictures of all liver diseases and their variations in dogs and cats.

METHODS

In cooperation with and under the auspices of the the Board of the World Small Animal Veterinary Association (WSAVA), an international Liver Standardization Group was formed, consisting of internationally recognized scientists in hepato-gastroenterology. Both liver-specialized pathologists and expert clinicians were invited from the USA, Europe, and Australia. In addition we have invited one of the top human liver pathologists, as an independent back up and to help in deciding about difficult topics. The Liver Standardization Group was not only formed under the auspices of the WSAVA, but also supported by the boards of the European and American Colleges of Veterinary Internal Medicine (ECVIM and ACVIM). The expert group was composed as follows:

Dr. S. Bunch (USA), clinical hepatologist

Dr. J. Charles (Australia), liver pathologist

Dr. J. Cullen (USA), liver pathologist

Dr. V.J. Desmet (Europe, Belgium), human liver pathologist

Dr. T. van den Ingh (Europe, Netherlands), liver pathologist

Dr. T. VanWinkle (USA), liver pathologist

Dr. D. Twedt (USA), clinical hepatologist

Dr. R. Washabau (USA), gastroenterologist/hepatologist

Dr. J. Rothuizen (Europe, Netherlands), clinical hepatologist, coördinator of the group

This group has met twice a year over a three-year period. Each year there was a meeting during the American ACVIM forum and one during the European ECVIM congress. The agreements on standardization reached in the previous period were presented at the specialist meetings of the two congresses, so that the reactions of the veterinary specialists in the field could be incorporated in the final standards developed. The pathologists of the group have also presented of the consensus diagnostic criteria at the American and European Veterinary Pathology congresses.

The liver diseases were divided into four groups:

(a) Vascular liver disorders,
(b) Biliary tract disorders,
(c) Parenchymal disorders including stellate cells and Kupffer cells
(d) Neoplasia

An exhaustive list was made of all liver diseases in the four groups, and cases were collected in all centers participating in the standardization group. In several publications veterinarians from practice or academia were also invited to submit samples or other contributions.

Two months before the meeting the pathologists had exchanged representative samples of tissue of all these diseases. All veterinary pathologists had selected three cases of each of the diseases of which they had paraffin-embedded liver tissue available. They selected those cases based on their feeling that they were representative for the disease. If appropriate, they also selected representative cases of acute, subacute, and chronic stages, or mild, moderate, and severe stages. Since there should be the possibility for each pathologist to make specific stains of liver slides, each participating center submitted four unstained slices of each selected tissue. Each pathologist thus possessed an identical set of slides of all diseases (ten or more cases per disease), so that it was possible to evaluate them in the months before the meeting, and to start to discuss them over the telephone and e-mail in preparation of the meeting. This ended up in the production of hundreds of slides by all pathologists.

During the meeting the members of the Liver Standardization Group evaluated all slides and the relevant clinical aspects of the diseases. Although there was a lot of discussion about the cases, it was not hard to reach consensus. A smaller selection was made from all slides that were considered to represent the typical features for all diseases. Ted van den Ingh has made a collection of the typical slides for all diseases for publication in this book.