GENERAL CHARACTERISTICS OF DBP

	Man	Rat	Chick
Molecular weight	56000	52000	60000
Sedimentation coefficient	4.1 S	4.1 S	4.1 S
Amino acid analysis	known	known	known
Electrophoretic mobility	alpha	alpha	beta
Isoelectric point	± 5	± 5	± 6
Thermostability increased by excess ligand	+	+	+
Binding characteristics K_a for 25OHD$_3$ (4C,pH 7.4)	$10^8 M^{-1}$	$10^8 M^{-1}$	$10^8 M^{-1}$
n binding sites	1	1	1
Tendency to polymerisation	-	+	-
Interaction with a cytosolic protein	+	+	+

The concentration of DBP is high in the three species (6 to 13 μM) so that less than 3% of all binding sites are normally occupied. The regulation of the serum concentration is quite dissimilar in the three species. There is little age-dependent variation in man and chick but an important increase in serum DBP in the growing rat. Estrogens increase the DBP level in man (and probably also the chick) whereas in the rat androgens increase the DBP concentration. The vitamin D status does not influence the DBP level in any of the species. Human and rat DBP are genetically heterogenous, coded by a pair of codominant autosomes. Human DBP was therefore previously known as "group-specific component or Gc".

The significance of the serum transport protein for vitamin D can probably be searched in its high affinity and high capacity for 25-hydroxyvitamin D. DBP therefore functions as a storage protein accumulating 25-hydroxyvitamin D during periods of access to vitamin D and releases it, thereafter, very slowly for biological activation or inactivation in the kidney. DBP is also very important in the placental transfer of 25-hydroxy-vitamin D: since the human neonatal DBP level is only half that of the mother, the neonatus also has only half the circulating reserve of 25-hydroxyvitamin D. The DBP level remains constant in most diseases, except in cirrhosis of the liver and nephrotic syndrome. Hypovitaminosis D occurs in the latter disease due to the continuous loss of 25-hydroxyvitamin D together with the loss of DBP in the urine.

Serum DBP also interacts with an ubiquitous intracellular protein to form the 6S intracellular binding protein but the significance of this complexation remains to be explored.Finally, DBP is also used in the competitive protein binding assay to measure 25-hydroxyvitamin D in biological fluids. This assay is especially useful to detect (latent) hypovitaminosis D and vitamin D intoxication.

VIRUS REPLICATION - AN INTRODUCTION

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Viruses can only multiply in an internal cellular environment. They lack subcellular organelles such as nuclei, mitochondria, ribosomes as well as cytoplasmic components that are necessary for the synthesis of their own structural components: nucleic acids (RNA or DNA), proteins, carbohydrates and lipids. Thus, viruses cannot multiply but must be replicated by the cells that they invade. The essential steps of virus replication are similar for all virus classes: first, a virus particle (virion) must attach to the outer surface of the host cell. Next, it penetrates the cell membrane and enters the cytoplasmic environment. Some or all of the outer surface layers of the virus (envelope and capsid) are removed, so that the viral genome (DNA or RNA) becomes accessible to the cellular organelles and enzymes which will initiate the replication process. Some of the genetic information is used to synthesize virus-specific enzymes (polymerases) which are necessary for the replication of the viral nucleic acid. Other parts of the viral genome code for the structural proteins. The newly synthesized viral nucleic acid and proteins are then assembled (maturation) into new viral particles which may leave the cells either by simple cell lysis or by a budding process at the membranes of the outer cell surface or in the endoplasmic reticulum.

This basic strategy of virus infections leaves ample space for variations depending on whether the viral genome is composed of DNA or RNA, on whether it is double- or single-stranded, linear or circular, monolithic or fragmented. The parental RNA may either be directly used by ribosomes (+ strand viruses), or it may first need transcription into a complementary strand (- strand viruses). Enveloped viruses probably require the synthesis of specific carbohydrates and lipids.

Depending on the genetic make-up of the host cell and on the conditions of infection, the virus cycle may be productive (i.e. many new infectious particles are released by each infected cell) or it may be restrictive, or even abortive.Some viruses may remain latently present in cells over a long time and over a large number of generations. Several mechanisms for such chronicity of virus infection have been discovered. Certain taxa of viruses have the unique capability to integrate their genome, or a fragment thereof, into that of the cell. Chronic infections may also be maintained by the generation of defective-interfering (DI) particles, which contain only part of the virus genome, but which are replicated when they are present in cells, along with complete virus particles. In general the small size of the DI-genome allows it to be replicated more rapidly than the intact genome and hence competes strongly for the polymerases. In certain conditions, DI-particles can alter the lytic pathway of infection and rapidly establish persistent infections in which the cells survive but carry in them considerable amounts of virus antigens. This is an important area in virology to-day as it may be related to the development of long-term degenerative diseases which may have a viral etiology.

SLOW VIRUS DISEASES OF THE CENTRAL NERVOUS SYSTEM

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During the last 3 decades a new concept of an infectious process has been derived by studying certain Central Nervous System (CNS) diseases in animals. These infections are characterized by an incubation period lasting for many months to years and by a predictable, protracted clinical course usually leading to death. It has been found that these disorders, which are refered to as slow virus diseases, are related to unconventional and conventional agents, both of which have been associated with naturally occurring diseases in animals and man. The unconventional agents, which have not been visualized, isolated or characterized reveal unusual biological and physico-chemical properties, unlike any known virus group. These agents are associated with scrapie in sheep, encephalopathy in mink and Kuru or Creuzfeldt-Jakob disease in man. The conventional viruses isolated from slow virus diseased brain material, such as Visna, Subacute Sclerosing Panencephalitis (SSPE). Progressive Rubella Panencephalitis (PRP) or Progressive Multifocal Leukoencephalopathy resemble classical viruses with typical structural, physico-chemical and biological characteristics. For this group of viruses, progress has been made in the understanding of the infectious process, since the isolates provide an experimental basis for virological and immunological studies in these diseases.

From a pediatric point of view, only SSPE and PRP are of interest, since the other slow virus diseases are usually not seen in children. SSPE is caused by a measles virus infection. Measles virus (refered to SSPE virus) has been isolated from CNS and lymphoid tissue. Moreover the patients reveal a pronounced antimeasles hyperimmunresponse which is pathognomonic for this disorder.

Virological studies indicate that SSPE viruses are related but not identical with typical virus isolated from acute measles. At the present state of investigation, SSPE is considered a late complication of acute measles infection. PRP is associated with a persistent rubella virus infection of the CNS. Virological and immunological data reveal great similarities to SSPE. However, information on the pathogenetic mechanism of this disease process are not available.

Previous investigations on slow virus diseases have demonstrated the different ways a virus infection can result in a chronic CNS disorder. Moreover, they have shown that virus-host interactions exist which lead to diseases lacking the common characteristics of an infectious process. Obviously, many virological and immunological problems have to be solved before the complexity of these disorders are understood, but it already can be expected, that other human diseases will be found which are caused by a slow virus infection.

VIRAL INFECTIONS OF THE CENTRAL NERVOUS SYSTEM AND LOCAL SYNTHESIS OF OLIGOCLONAL ANTIBODIES

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Oligoclonal IgG, synthesized locally in the central nervous system, is commonly demonstrable in the cerebro-spinal fluid in subacute sclerosing panencephalitis and some other viral central nervous system infections and in multiple sclerosis.

Extensive studies of cerebro-spinal fluid and brain tissue in subacute sclerosing panencephalitis showed that the bulk of the oligoclonal IgG is measles virus-specific antibody. A principally similar association of oligoclonal cerebrospinal fluid-IgG with virus-specific antibody activities was observed in progressive rubella virus panencephalitis, herpes simplex encephalitis and mumps meningitis. These findings indicate that the occurrence of oligoclonal IgG in the cerebro-spinal fluid in viral central nervous sytem infections reflects a specific antibody response to virus antigens in the central nervous system.

In some cases of subacute sclerosing panencephalitis and other central nervous system infections, a local synthesis of small amounts of oligoclonal antibodies to viruses other than that causing the disease was observed. This suggests that the immunizing drive caused by a virus infecting the central nervous system sometimes may lead to an activation of cell clones producing antibodies to unrelated antigens. Such mechanisms may be relevant in explaining the local synthesis in the central nervous system of oligoclonal antibodies to various viruses in multiple sclerosis.