Clinical Biochemical and Hematological Reference Values in Normal Experimental Animals

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PREFACE

The purpose of this book is to make available to the research worker in medicine and biology a collection of reference chemical, physiological, and hematological values in commonly used experimental animals.

The book emphasizes the major factors which influence the establishing of normal or reference values. Factors including collection, processing, and storage of specimens, methods and procedures, units of measurement, effects of drugs and toxicological agents, and effects of pathological conditions are discussed in detail. Clinical biochemical and hematological data on 14 species of experimental animals are presented and compared with those values reported in humans.

We hope this book will be a useful source of information on clinical laboratory values in these experimental animals.

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Section I

Introduction

The main objective of this book is to present reliable and quality controlled data on clinical biochemical and hematological values of a wide variety of normal experimental animals used in biological and medical research. A compendium of normal values on several well-defined species and breeds of experimental animals should be quite valuable in providing reference data of commonly used diagnostic tests in hematology and clinical chemistry laboratories. Reference values of normal laboratory animals are useful in clinical and biological investigations in which experimental animals are used to study human diseases. The ranges of normal values for laboratory animals can provide criteria for the selection of appropriate experimental animal species, not only for the study of pathological conditions, but also for toxicological studies and for the understanding of mechanisms of disease processes.

Since a wide variety of experimental animals is currently used for medical research, it is rather difficult to establish a normal range of chemical constituents in blood, plasma, serum, and other body fluids of all the animal species. Normal values reported in the literature for a given species of animal often range so widely that the clinical investigator has no valid assessment of a particular animal's physiological state. In addition, the values reported are not comprehensive, and in most studies only a few unrelated biochemical and hematological data on some animal species have been reported.

A number of factors contribute to the problems of the establishment and use of normal values:

1. Arbitrary choice of population—lack of preselection and screening.
2. Lack of consideration of age, sex, breed, strain, nutritional and physiological status and environmental conditions of the experimental animals.
3. Lack of consideration of physiological and analytical variation.
4. Varying statistical interpretation of data—a) assumption of normal distribution of values for the population, b) use of empirical limits to establish normal range.

The data presented in this book have been collected with these criteria in mind. Analytical variations were minimized by using standard quality control methods, including the use of replicate standard sera and analysis of the same specimen with different test methods at different time intervals. Physiological variations were considered by defining and selecting animal test populations. Different age groups, sexes and breeds of

animal species were used to determine the normal range of clinical biochemical and hematological values. The nutritional and environmental status of the animals was kept constant throughout these studies.

Standard methods of sample collection, storage, and preparation are described in Section II, and the methods of biochemical determination used throughout these studies are described in Section III. To eliminate systematic errors and to improve the precision and specificity of our methods, a broad-range concept of quality control was applied. Items considered included standardization of tests, precision, specificity, recovery studies, interlaboratory comparisons, and long-range stability of laboratory performance (Levey and Jennings, 1950; Hoffman and Waid, 1963; Waid and Hoffman, 1955; Henry, 1959, 1974; Wirth and Thompson, 1965; Neumann, 1968; Martinek *et al* 1968; Corley, 1970; Zieve, 1966; Caraway, 1971; Amador *et al* 1968; Moss *et al* 1971). Most values presented here are indicative of a mean value for the population available for testing. In general, these mean values agree with those reported in the literature (Coffman, 1970; Coles, 1973; Jennings and Mulligan, 1953; Kanenko and Cornelius, 1970; Medway *et al*, 1969; Laird, 1972; Altman and Dittmer, 1971, 1974; Burns and DeLannor, Jr., 1966; Albritton, 1952).

The currently held concept in human clinical medicine of applying two times the standard deviation as the normal ranges for a given group of animals was applied because the populations were carefully selected with regard to age, sex, breed, and nutritional conditions of animals showing good normal distribution curves (Section V). It has been reported that qualitative values for a given animal from a given species are strongly influenced by age (Laird and Fox, 1970), sex (Fox *et al* 1970; Laird *et al*, 1970), breed (Coles, 1973), strain (Fox *et al* 1970; Laird *et al* 1970), environment (Roussel *et al* 1971), and the physiological status of the animal (Laird and Fox, 1970; Fox *et al* 1970).

Although intraspecies physiological variation contributed to the range of biochemical and hematological values, it could be minimized by selecting genetically pure populations of animals that are kept under constant environmental and nutritional conditions. Interspecies physiological variations of the animals, on the other hand, show large ranges of normal values because of inherent physiological differences. The physiological and other biological characteristics of some animal species and man are compared in Tables 1-3. These values may be useful in selecting an animal species as a model for the study of human disease. The data may also be useful in choosing between laboratory tests in experimental animals.

In human medicine the purpose of hematology and clinical chemistry laboratory results is to aid the physician in making decisions in the diagnosis and treatment of patients. A critical aspect of the use of laboratory data is their interpretation. Therefore normal or reference values in various populations of subjects, or in pooled specimens from representative populations, should be established by every laboratory, keeping in view the many variable factors—analytical as well as biological.

Individual laboratory tests are subject to a number of variables, and the physician and clinical investigator should be aware of this variability in his interpretation of any changes which he may note. Physiological parameters may fluctuate considerably. Diurnal, annual, and postural variations in plasma constitutents of experimental animals (and man) have been well documented.

Table 1. Comparative Biological Data of Experimental Animals and Humans

Species	Average Life Span (years)	Age at Puberty	Chromosome No. (Diploid)	Average Estrus Cycle (days)	Average Gestation Period (days)	Litter Size
Mouse (*Mus musculus*)	4	35±5.0 days	40 s	4	25	1-12
Rat (*Rattus norvegicus*)	5	50±10.0 days	42 m	4.5	21	1-9
Hamster (*Mesocricetus auratus*)	1.9	45±11.0 days	44 m	4	18	2-12
Guinea pig (*Cavia porcellus*)	6	62±8.0 days	64 m	18	68	1-8
Rabbit (*Oryctolagus cuniculus*)	13	7.0±1.5 months	44 s	Induced Ovulation	30	1-13
Chicken (*Gallus domesticus*)	24	--	78 s, 770	--	--	--
Cat (*Felis catus*)	23	10.5±3.5 months	38 m	22	63	1-6
Dog (*Canis familiaris*)	22	7±1 months	78 m	9	61	1-12
Monkey (Rhesus) (*Macaca mulatta*)	29	2.5±1.5 years	42	28	168	1
Pig (*Sus scrofa*)	27	7±1.5 months	40 s	11	114	4-6
Goat (*Capra hircus*)	17	8±2 months	60 s	21	151	1-5

Table 1 (con't.). Comparative Biological Data of Experimental Animals and Humans

Species	Average Life Span (years)	Age at Puberty	Chromosome No. (Diploid)	Average Estrus Cycle (days)	Average Gestation Period (days)	Litter Size
Sheep (Ovis aries)	20	7.5±1.5 months	54 m	17	150	1-4
Cattle (Bos taurus)	30	8±2 months	60 m	18.5	280	1-2
Horse (Equus caballus)	50	10±2 months	64 m	24	330	1
Man (Homo sapiens)	73	13.5±2.5 years	46 s,o,m	28.4	278	1

S = Spermatogonium; O = oogonium; m = somatic cell.

Source: Hafez (1970, 1971, 1974); Altman and Dittmer (1974); Peplow et al (1974).

Table 2. Physiological Characteristics of Experimental Animals and Humans

Species	Body Wt (kg)	Surface Area (cm^2)	Energy Metabolism		Cardiac Function					Arterial Blood Pressure (mm Hg)	
			cal/kg/day	cal/m^2/day	Heart Wt (g/100g)	Heart rate (beats/min)	Stroke Vol (ml/beat)	Cardiac output L/min	Cardiac index L/m^2/m	Systolic	Diastolic
Rat	0.1-0.5	0.03-0.06	120-140 (B)	760-905 (B)	0.24-0.58	250-400	1.3-2.0	0.015-0.079	1.6	88-184	58-145
Rabbit	1-4	0.23	47	810	0.19-0.36	123-330	1.3-3.8	0.25-0.75	1.7	95-130	60-90
Monkey	2-4	0.31	49 (B)	675	0.34-0.39	165-240	8.8	1.06	---	137-188	112-152
Dog	5-31	0.39-0.78	34-39 (B)	770-800 (B)	0.65-0.96	72-130	14-22	0.65-1.57	2.9	95-136	43-66
Man	54-94	1.65-1.83	23-26 (B)	790-910 (B)	0.45-0.65	41-108	62.8	5.6	3.3	92-150	53-90
Pig	100-250	2.9-3.2	14-17 (B)	1100-1360 (B)	0.25-0.40	55-86	39-43	5.4	4.8	144-185	98-120
Ox	500-800	4.2-8.0	15 (B)	1635 (B)	0.31-0.53	40-58	244	146	---	121-166	80-120
Horse	650-800	5.8-8.0	25 (R)	2710-2770 (R)	0.39-0.94	23-70	852	188	4.4	86-104	43-86

B = Basal; R = Resting

Source: Swenson et al (1970); Altman and Dittmer (1971, 1974); Coles (1973); Phyillis (1976).