OF PIGS AND MEN AND RESEARCH:

*A Review of Applications and Analogies of the Pig, sus scrofa, in Human Medical Research**

WILLIAM RICHARD DOUGLAS

Dept. of Clinical Chemistry, Rigshospitalet, Copenhagen, Denmark

(Received 4 October, 1971)

Abstract. A review of the role of pigs as an ideal experimental animal in human medical research is given, covering applications and analogies of sus scrofa in general medicine encompassing space medicine. It is also a report of some investigations carried out on Danish Landrace pigs that emphasize the similarities of swine and men. The musculoskeletal system, respiration, circulation, blood, lymph, digestion, metabolism, nutrition, excretion, endocrines, dermatological problems, and eyes are discussed along with other aspects to show the value of the pig when a large, human-like biomedical research animal is needed.

Just a few papers (Landy *et al.*, 1961; Bustad, 1966; Bustad and McClellan, 1966) during the past decade have elaborated on the potentialities of swine as ideal experimental animals for medical research and shown that pigs are not just pigs, but almost humans. Although everyone can differentiate between the physical appearances of pigs and men, not everyone can visualize the similarities and applications of pigs to men. Nor can everyone realize the strikingly long list of biological analogies that establish the pig as physiologically the nearest animal to man with very few exceptions. Socially, porcine animals are usually placed at the bottom level, that position that human beings least want to emulate. Generally, pigs are relative outsiders to the medical research laboratories. All this is notwithstanding the two species such as rat and man, differ tremendously in size, life span, overall metabolic rate, nature of their diet, and nutritional requirements.

In most instances herein, reference is to the Danish Landrace pig which may be considered a 'genetically-created' and 'commercially-bred' long bodied, thick-boned, slab sided, level backed, minimum fat, light shouldered, small footed cross between a native strain and a British Large White Pig with an estimated 70% muscle tissue. Nevertheless, in much of the reported data, application can be made to almost all pigs belonging to the order of mammals known as artiodactyla or even-toed ungulates in the sub-order Suiformes, species: sus scrofa.

During a series of field and laboratory experiments designed to study overall porcine biochemistry, incidental observations were made of over 200 pigs and it is the relevant observations reviewed and discussed herein. For human medical research,

* Most of the findings and work reported here was carried out while Senior Research Scientist at the Danish Meat Research Institute, Roskilde, Denmark. Reprint requests should be directed to Postbox 67, DK-1003 Copenhagen K, Denmark.

Space Life Sciences **3** (1972) 226–234.

whether the blood and lymph, or circulation, respiration, excretion of urine, digestion, metabolism, nutrition, endocrines, nervous system, vision, or various categories of space medicine, it appears that the pig is the ideal experimental animal.

Randel (1971), Busby (1970), Busby (1968), Douglas (1970), Douglas (1969), Brodzinsky *et al.* (1971) and Parin and Kosmolinsky (1971) among others, point out the unsolved problems of man in flight and the need for intensified study of the human body. At the same time there is the almost unuttered desire for the most perfect research animal that is most like the human. Mountain or altitude sickness which is recognized as a real disease entity in humans going above 10000 ft from low altitudes may cause acute disabling respiratory distress. Swine react similarly to man and are altitude sensitive. Exploring the ability of animals to make environmental adjustments is important (Wunder, 1966) and with such a large test animal the effects of acute acceleration upon man can shed light on decreased saturation of blood with oxygen presumably due to gravitationally induced shunting of blood or due to uneven expansion of alveolae, or decreased lung volume cases. Systems for supply, removal, or recycling of respiratory gases may be first tried on pigs. Continued exhaustive studies of hypoxia can well utilize the pig. In observing the respiratory system of swine shortly after food intake, the breathing rate was 10–16 per minute, comparable with the 10–14 per minute in relaxed humans. The pig could also be utilized to further test the miniature respiratory rate and volume sensor developed for hyperbaric, pure oxygen atmosphere environments (Lewis and Rezek, 1970). Applications of porcine animals to space ecology, exobiology, and to life in extra-terrestrial environments are too numerous to list (Douglas, 1969; Freundlich and Wagner, 1969).

The pig life span of two decades is long enough to allow measurement of the effects of radiation in shortening life and in causing malignancies. One scientific result of the space programs of the National Aeronautics and Space Administration (U.S.A.) and the Academy of Sciences of the U.S.S.R. as reported to the International Committee on Space Research (COSPAR) in the 12th Plenary Meeting, 1969, has been the discovery of the Van Allen Radiation Belt. Assessments of the presently known and anticipated radiation hazards in space are indicating that serious acute radiation effects should not be suffered by astronauts if adequate precautions are taken. However one must remember that current information on ionizing radiation, particularly from solar flares in space, is based on relatively sparse data. Therefore it is still necessary to treat radiation as a problem. The spherical shell around the Earth of trapped (Van Allen) radiation is considered a somewhat minor hazard, but the radiation zones around planets being explored are yet to be identified and studied. No data exists regarding radiation on the planet Venus. The problem is that human effects have been studied for only one or two generations and our knowledge of the cumulative effects of small doses is considerably less than our knowledge of the acute effects of high doses. In view of the impracticability of using men as test subjects, and the questionable recommendation of further using male Macaca Nemestrina as test subjects, it seems worthy to propose the employment of Danish Landrace

Pigs or a well-bred strain of any miniature pig as an ideal test subject because of the striking similarities of swine and human biology.

The teeth of the pig are human-like, usually 20–25% larger, consisting of molars and cutting teeth. On the basis that swine start with deciduous teeth and shed them as permanent teeth develop, one could deduce that the pig's mouth and jaw provide a model that makes possible investigations on dental problems of children, on chewing processes, on tooth movements in biting, in addition to assessing the functioning of orthodontic appliances. No other animal approximates man in the development, size, and physiology of the teeth, not so specifically in the Danish pigs, but more so with certain domestic strains in the United States.

An operation on the gastro-intestinal tract of the pig is identical to the surgery performed on a human subject. Many have remarked about the convenience for studying the functioning of the pancreas, the digestive system, the role of vitamins, and metabolism (Douglas, 1968; Bustad, 1966; Landy *et al.*, 1961; Bustad and McClellan, 1966; Brown, 1963) and speculated over the intestinal resemblance to man as the reason accepted for using pigs as experiment-animals for evaluating dietary effects on physiological systems. Animal metabolic studies of calcium, strontium, copper, zinc, as well as studies of divalent cations are fitted for such an experimental model as the pig (Comar and Bronner, 1964; Douglas, 1968), especially with germ-free pigs (Coates, 1968). The pig with his capacious mouth, large stomach, long small intestine, and large intestine about six times the length of the animal's body, is the only ideal subject for nutrition studies.

The eye of the Danish pig is almost identical to the human eye. It is highly developed, and the retina is rich in short, thick cones. The retina, pupil, and lens in both men and pigs are alike, but seldom does the Scandinavian pig strain have anomalies and malformations observable in the eye, nor does he have congenital anophthalmos. More use consequently should be made of this association, for example in answering the question of dietary stress on the normal function of the lens or, possibly the evaluation of the eyes following exposure to low energy X-rays.

The skin of pigs and men is almost indistinguishable by physiological, anatomical, and physical resemblance, with the human having slightly thinner skin. Similar proteins occur in both (Bustad and McClellan, 1966). In both there occurs a sparse hair coat, a thick epidermis that has a well differentiated undersculpture, a dermis that has a well-defined papillary body, and most noteworthy, both have a large content of elastic tissue. The pig is the only animal in the world except man that can sunburn. Designed research using the pig can perhaps provide the necessary data on the sensitivity of various animal species to neutron irradiation for a rational assessment of exposure guidelines for individuals exposed to a nuclear detonation under emergency conditions. Measurements of the epidermis turnover time in swine at various ages may indicate whether a correlation exists between age and turnover time.

The biliary system of the pig duplicates that of the human body. Surgeons involved in research have in the past attempted to utilize this fact by trying to produce distension of the biliary system by partial occlusion of the common bile duct for construction of a hepaticojejunostomy. It is already an accepted procedure to use pig liver perfusion as a mode of therapy for certain patients in hepatic coma, and this therapeutic use of heterologous liver perfusion allows for following many here-to-fore unclarified problems, such as the dissociation curve of hemoglobin and oxygen, the albumin synthesis by both pigs and patients, and the effect of the pig liver perfusion on the hyperdynamic cardiovascular state and arteriovenous oxygen difference and partial pressure of oxygen in arterial blood. Studies on the isolated perfused liver point out its usefulness in following glucose and protein metabolism, as well as utilizing it as an ex-vivo perfusion system in the support of hepatic failure in hospital patients. To see the influences which control hepatic lymph formation in the isolated, perfused organ, comprehensive studies could be done on the isolated, perfused pig liver. Liver transplantation in the pig may prove to be a useful model for analysis of immunological mechanisms in the biology of transplantation (Calne *et al.*, 1967). It was apparent by observation that liver lobules of the Danish pig are coated by rather heavy connective tissue septa which give a lobulated appearance to the surface of the porcine liver, whereas humans have much less interlobular connective tissue.

Again because of similarity, one of the fields in which the pig will make its greatest contribution to human health and longevity is that of research on the heart and circulatory system. The coronary artery anatomy of the pig is very uniformly a duplicate of man, yet researchers in pulmonary hypertension are taking little advantage of the fact that the cardiovascular physiology of the pig is unexploited. The resting heart rates of men are 60–90 beats per minute, and in 6-month old pigs examined in Denmark, 65–80 beats per minute. Pigs may be useful in investigating the treatment of arrhythmias in myocardial infarction, in studying atherosclerosis, and in evaluating the effects of increased wall tension, increased wall size, anabolic and anti-anabolic agents, hypoxemia, myocardial stress, and decreased cardiac work on the rate and extent of collateral vessel development following induced experimental myocardial infarction. In order to evaluate effective and ineffective collateral blood flow more precisely, a comparison of coronary blood flow and the collateral vessel development visualized can be made after gradual right coronary occlusion using the farm pig as the experimental animal. The gradual right coronary occlusion was produced at thoracotomy by placing an aneroid constrictor around the right coronary artery distal to the conal branch. Although this project was never completed, it was intended that a direct correlation between visualized neo-vascularization, coronary blood flow, and size of the myocardial infarction would better define what effective coronary collaterization was. In another way, the hemophilia-like swine are excellent experimental models for the study of hemostasis problems. Some similarities are pointed out in Table I. Concerning this field of the heart and circulatory system, there is a moderate amount of pertinent literature (Frandson, 1965; Dukes, 1955; Booth *et al.*, 1966; Bustad and McClellan, 1965; Scarborough, 1931; Mustard *et al.*, 1963; Christensen and Campeti, 1959; Wintrobe, 1961; Schalm, 1965; Douglas, 1968). Finally, there is especially needed a quantitative measure for the degree and extent of

TABLE I

Some laboratory similarities of pigs and men

Analysis	Pigs	Men
Red blood cell volume	46%	46%
Hemoglobin in blood	14.5 g/100 ml	14.5 g/100 ml
Mean corpuscular hemoglobin concentration	33%	34%
Serum calcium	2.7 mmol/l	2.6 mmol/l
Serum protein	80–98 g/l	70–85 g/l
Serum inorganic phosphate	1.7 mmol/l	1.4 mmol/l
Plasma bicarbonate	18–25 mmol/l	21–26 mmol/l
Serum chloride	99–105 mmol/l	98–108 mmol/l
Serum sodium	140–150 mmol/l	136–147 mmol/l
Serum potassium	4.9–5.5 mmol/l	3.6–4.9 mmol/l
Plasma copper	ca. 110 ug/100 ml	ca. 116 ug/100 ml
Arterial blood pH	ca. 7.3	ca. 7.4
Icterus index	4–5 units	4–6 units
Specific gravity of blood	1.050–1.061	1.048–1.066
Fasting plasma glucose (at birth)	ca. 4.3 mmol/l	3.9–6.6 mmol/l
Serum aspartate aminotransferase	17–45 Frankel units	15–37 Frankel units

atherosclerosis, particularly that found in the coronary arteries (Siegel *et al.*, 1970).

Little is known of the animal nervous system but some studies have been carried out by Platt and Stewart (1960).

Human red muscle is indistinguishable from pig muscle. In 1963 – 1965, an extensive investigation of porcine muscle tissue was done to study glycolysis, to study certain subcellular particles of muscle tissue, and to try to understand the biochemistry of these tissues. In addition there was interest in determining the factors responsible for tissue structure variations reported in Denmark. Porcine muscle mitochondria were obtained by both differential centrifugation and chromatographic sieving isolation procedures (Hjerten, 1962; Hjerten, 1964) from fresh post-mortem loin muscle removed from the 10th to 15th thoracic region of 20 Danish Landrace pigs, under 0–5 °C temperature conditions and kept in 10% suspension with Tris-KCl medium at pH = 7.4. Employing a sequence of phase contrast microscopic evaluation of morphological alterations during 0–30 minute observations of fresh unfixed suspensions, a differential count of mitochondrial types and forms in a 11.2% buffered formalin-fixed sample (Harman and Kitiyakara, 1955), and measurement of Succinate Dehydrogenase (1.3.99.1) activity by a colorimetric method involving ferricyanide reduction (Singer *et al.*, 1965), it was found that these porcine samples of mitochondria were 0.5–4.0 μm in length and 0.2–0.4 μm in diameter. These prepared mitochondria were indistinguishable from human preparations. Additionally, the longissimus dorsi muscle of the animals examined were similar structurally to the latissimus dorsi muscle in man. This latter observation is based on direction of muscle fibers, arrangement of the tendons, the synovial membranes, and the appearance of accessory structures under microscopy. For a further analogy, protein determinations of this muscle tissue were carried out by the Biuret Method (Douglas, 1965) with the result that the adult skeletal muscle tissue of these pigs gave equivalent results to human tissue. It is known that muscle tissue in the adult human skeleton has a range 1.26–2.58% creatine, calculated as percent of the crude protein found and that correlated with this finding in which the range was 1.82–2.36% for 20 pigs. In follow-up studies of these isolated cell organelles, it was possible to demonstrate the Embden-Meyerhof glycolytic pathway, just as if they were from a human source, and this meant carbohydrate metabolism research could be done. For example, in the neonate, the use of the newborn piglet as a model system permits tissue analysis that may provide important data in studying the human infant since all species of the pig are highly developed at birth. The rapid development of resistance to starvation hypoclycemia in the pig at 3–5 days of age provides a unique opportunity for research-minded pediatricians to determine critical factors in perinatal adaptation. Discussion of various aspects of porcine muscle appears in many publications, but special attention should be drawn to the reports of Davey, (1960), Cassens *et al.*, (1963), Lawrie, (1961), Bate-Smith and Bendall, (1956), Chappell and Perry, (1953), Furminger, (1964), Scopes, (1964) and Elliott, (1965).

In no other animal does stress influence disease more than it does in the pig, and often the animal is found to be suffering from two diseases at the same time, one of which may have been latent for weeks, such as an onset of acute pneumonia in swine suffering from virus pneumonia. The transmissable gastroenteritis virus of swine could serve as a model for the study of human malabsorption. Shilov (1970) has pointed out some needs for more knowledge about microbes and space flight. Kenworthy (1971) has proposed the use of gnotobiotic pigs for research on enteritis associated with escherichia coli. Takatsy *et al.*, (1969) have presented data on the susceptibility of pigs to Influenza B Virus. Norris and Harper (1970) have summarized much of the knowledge on Foot and Mouth Virus. At this stage, a minimal of comparative data exists in microbiological sciences.

Price and collaborators as far back as 1956 have shown that the 8-methyl ether of xanthurenic acid has been identified in the urine of humans and swine yet has not been detected in the urine of rats or other species (Roy *et al.*, 1961). This has long been an amino acid phenomenon. This new excretion product lends mystery to the pathway of biosynthesis of this quinoline derivative and adds further complications to the tryptophane metabolism pattern. Observations of collective studies on pigs over a two year period has consistently shown that the amino acid composition of the body proteins was unaffected by diet.

It being common knowledge to the biochemist that the activity of a tissue is determined by its enzyme content and all enzymes being protein in nature, makes the rich tissue sources of porcine and human enzymes strikingly unlike those in rat, mouse, guinea pig, rabbit, dog, cat, pigeon, horse, and ox. Specifically and most outstanding are the Monoamine Oxidase (1.4.3.4.) in liver, and the two hydrolases, Amylase (3.2.1–) and Lipase (3.1.1.3) in pancreas. Monoamine oxidase which plays an important part in the metabolism of the brain amines is inconclusively investigated. It is puzzling that when 3246 sera from Danish Landrace pigs were subjected to starch gel electrophoresis, it was observed that all sera exhibited one of six amylase phenotypes (Heeselholt, 1969) yet in human enzyme measurements there are no such claims to date. Pancreatic lipase which has the function of splitting triglycerides in stepwise fashion to fatty acid and glycerol at rates depending on the fatty acid composition, was found by Ammon and Jaarma (1950) to exhibit high activity and only evident in men and pigs.

Certainly during the past few years the pig has gained significant importance as a laboratory test animal in medical research and investigators have selected this animal in studies on organ transplantation and the mechanism of xenograft rejection. Gross anatomic features of the porcine kidney are well suited for transplantation to other mammalian species also. Not much yet has been followed by physiologists of renal function and nephron structure in view of the pig kidney being such an excellent biological model. Not much has been studied about the mechanism of lymph formation in the kidney. Renal physiology is similar to man in nephron type, maximal urine concentration, and many respects, as pointed out in Table II. The specific gravity of

TABLE II

Some anatomical and functional aspects of renal physiology in the pig, the dog, and man (Data from Nielsen *et al.*, 1966)

Data	Pig	Dog	Man
Percentage of 'long-looped' nephrons	3	100	14
Relative medullary thickness (RMT) $\text{RMT} = \frac{\text{medullary thickness} \times 100}{\text{kidney size}}$	1	4.3	3.0
Maximum urine concentration (dehydration), maximal osmolal concentration per kg	1080	2425	1160
Maximal urine/plasma osmolal ratio	3.7	7.4	4.0
Acetylation of *p*-aminohippurate	+	none	+
Filtration fraction (ratio of glomerular filtration rate to effective renal plasma flow)	0.26	0.32	0.20

urine is 1.010–1.030 normally in man and in the Danish Landrace pigs (Douglas, 1968) 1.010–1.050. Hodson, *et al.*, in 1969 reported extensive accounts of experimental obstructive nephropathy in the pig and concluded that most of the phenomena encountered in their work had already been observed in man.

Apart from the biological side, the pig must not be considered stupid. The pig can be used for the observation of many well-defined patterns of individual and group behavior, as pointed out by Hafez (1969). The pig has the highest incidence of mammalian intersexuality (Armstrong and Marshall, 1964). Cytogenetics has repeatedly verified that the techniques of chromosome analysis applicable to the pig are similar to those described for the human. The karyotype of the pig consists of 38 chromosomes which are easily grouped on a morphologic basis, and certain of chromosomes are individually identifiable (Bustad and McClellan, 1966).

Acknowledgements

I am deeply indebted to Dr Mogens Mandrup for veterinarian advice, to Mr T. Wichmann Jörgensen for much agricultural information, to Mr Mogens Jul and Mr Niels-Henrik Hansen, directors of The Danish Meat Research Institute for the material originating from that institution. I am also grateful to the Roskilde Andels Svineslagteri in Roskilde, Denmark for permitting me to take porcine muscle samples in 1964. The author is indebted to Dr Jörgen Kieler and his staff of Fibiger Laboratory, Copenhagen, for providing advice and laboratory facilities for the mitochondria preparations, and to Dr Jerker Porath and Dr Stellan Hjerten of the University of Uppsala, Sweden, for technical assistance and advice on the chromatographic sieving isolation procedures.

I have assumed sole responsibility for presenting what I consider to be pertinent and reliable information in this report. The opinions or assertions contained herein are the private views of the author and are not to be construed as official or as reflecting the views of the Danish Meat Research Institute or the Fibiger Laboratory or the University of Uppsala or Rigshospitalet.

References

Ammon, R. and Jaarma, M.: 1950, in *The Enzymes* (ed. by J. B. Sumner and K. Mybäck, Vol. 1. Part 1, Academic Press, New York, p. 390.

Armstrong, C. N. and Marshall, A. J.: 1964, *Intersexuality in Vertebrates Including Man*, Academic Press, London.

Bate-Smith, E. C. and Bendall, J. R.: 1956, *British Med. Bull.* **12**, 230–235.

Booth, N. H., Bredeck, H. E., and Herin, R. A.: 1966, in *Swine in Biomedical Research* (ed. by L. K. Bustad and R. O. McClellan), Pacific Northwest Laboratory Richland,, Washington, p. 331–346.

Brodzinsky, R. L., Rancitelli, L. A., Haller, W. A., and Dewey, L. S.: 1971, *Aerosp. Med.* **42**, 621–626,

Brown, A. M.: 1963, in *Animals for Research* (ed. by W. Lane-Petter), Academic Press, London, p. 261–285.

Busby, D. E.: 1968, *Space Clinical Medicine*, D. Reidel Publishing Co., Dordrecht, Holland.

Busby, D. E. (ed.): 1970, *Recent Advances in Aerospace Medicine*, D. Reidel Publishing Co., Dordrecht, Holland.

Bustad, L. K.: 1966, *Scient. Am.* **214**, 94–100.

Bustad, L. K. and McClellan, R. O.: 1965, *Nature* **208**, 531.

Bustad, L. K. and McClellan, R. O. (eds.): 1966, *Swine in Biomedical Research*, Pacific Northwest Laboratory, Richland, Washington.

Calne, R. Y., White, H. J. O., Yoffa, D. E., Binns, R. M., Maginn, R. R., Herbertson, R. M., Millard, P. R., and Molina, V. P.: 1967, *British Med. J.* **4**, 645–648.

Cassens, R. G., Briskey, E. J., and Hoekstra, W. G.: 1963, *J. Food Sci.* **28**, 680–684.

Chappell, J. B. and Perry, S. V.: 1953, *Biochem. J.* **55**, 587–595.

Christensen, G. C. and Campeti, F. L.: 1959, *Am. J. Vet. Res.* **20**, 18–26.

Coates, M. E. (ed.): 1968, *The Germ-Free Animal in Research*, Academic Press, London.

Comar, C. L. and Bronner, F. (eds.): 1964: *Mineral Metabolism*, Vol. 2, Part A, Academic Press, New York.

Committee on Space Research: 1969, 12th Plenary Meeting, Prague, Czechoslovakia, May.

Davey, C. L.: 1960, *Arch. Biochem. Biophys.* **89**, 303–308.

Douglas, W. R.: 1965, *Scand. J. Clin. Lab. Invest.* **17** (Suppl. 86), 136.

Douglas, W. R.: 1968, unpublished report.

Douglas, W. R.: 1969, *Scand. J. Clin. Lab. Invest.* **24** (Suppl. 110), 64.

Douglas, W. R.: 1970, *Space Life Sci.* **2**, 151–157.
Dukes, H. H.: 1955, *The Physiology of Domestic Animals*, 7th ed., Bailliere, Tindall and Cox, London.
Elliott, R. J.: 1965, *Nature* **206**, 315–317.
Frandson, R. D.: 1965, *Anatomy and Physiology of Farm Animals*, Lea and Febiger, Philadelphia.
Freundlich, M. M. and Wagner, B. M. (eds.): 1969, *Exobiology*, American Astronautical Society, Washington, D.C.
Furminger, I. G. S.: 1964, *Nature* **202**, 1332–1333.
Hafez, E. S. E. and Signoret, J. P.: 1969, in *The Behaviour of Domestic Animals* (ed. by E. S. E. Hafez), Bailliere, Tindall and Cassell, London, pp. 349–388.
Harman, J. W. and Kitiyakara, A.: 1955, *Exp. Cell Res.* **8**, 411–435.
Hesselholt, M.: 1969, *Serum Protein Polymorphisms in Swine*, Munksgaard, Copenhagen.
Hjertén, S.: 1962, *Arch. Biochem. Biophys.* **99**, 466–475.
Hjertén, S.: 1964, *Biochim. Biophys. Acta* **79**, 393–398.
Hodson, C. J., Craven, J. D., Lewis, D. G., Matz, L. R., Clarke, R. J., and Ross, E. J.: 1969, *British J. Urology* **XL1** (6) Suppl., pp. 1–51.
Kenworthy, R.: 1971, *Proc. Roy. Soc. Med.* **64**, 436–439.
Landy, J. J., Growdon, J. H., and Sandberg, R. L.: 1961, *J. Am. Med. Assoc.* **178**, 1084–1087.
Lawrie, R. A.: 1961, *J. Agric. Sci.* **56**, 249–259.
Lewis, Jr., C. E. and Rezek, T. W.: 1970, *Space Life Sci.* **2**, 206–218.
Mustard, J. F., Rowsell, H. C., Murphy, E. A., and Downie, H. G.: 1963, *J. Clinical Invest.* **42**, 1783–1789.
Nielsen, T. W., Maaske, C. A., and Booth, N. H.: 1966, in *Swine in Biomedical Research*, (L. K. Bustad and R. O. McClellan, eds.), Pacific Northwest Laboratory, Richland, Washington, pp. 529–536.
Norris, K. P. and Harper, G. J.: 1970, *Nature* **225**, 98–99.
Parin, V. V. and Kosmolinsky, F.: 1971, *Aerosp. Med.* **42**, 339–340.
Platt, B. S. and Stewart, R. J. C.: 1960, *Proc. Nutr. Soc.* **19**, viii–ix.
Randel, H. W. (ed.): 1971, *Aerospace Medicine*, 2nd ed., Williams and Wilkins Company, Baltimore.
Roy, J. K., Price, J. M., and Brown, R. R.: 1961, *J. Biol. Chem.* **236**, 145–148.
Scarborough, R. A.: 1931, *Yale J. Biol. Med.* **3**, 547–552.
Schalm, O. W.: 1965, *Veterinary Hematology*, 2nd ed., Lea and Febiger, Philadelphia.
Scopes, R. K.: 1964, *Biochem. J.* **91**, 201–207.
Shilov, V.: 1970, *Aerosp. Med.* **41**, 1353.
Siegel, P. V., Mohler, S. R., and Cierebiej, A.: 1970, *Aerosp. Med.* **41**, 808–814.
Singer, T. P., Bernath, P., and Lusty, C. J.: 1965, in *Methods of Enzymatic Analysis*, 2nd printing, revised (ed. by Bergmeyer, H.-U.), Academic Press, New York, pp. 340–345.
Takatsy, G., Farkas, E., and Romvary, J.: 1969, *Nature* **222**, 184–185.
Wintrobe, M. M.: 1961, *Clinical Hematology*, 5th ed., Lea and Febiger, Philadelphia.
Wunder, C. C.: 1966, *Life Into Space*, F. A. Davis Company, Philadelphia.