polycythemia in animals (†,2) after chronic exposure to hypoxia for several weeks. Since the reticulocytosis in the present experiment is equivalent to that of chronic exposure, it may be concluded that ESF was produced in the animals during the 6 hour residence at 22,000 feet.

There were no significant changes from baseline values in the mean hematocrits of the heptal groups during the 4 days following acute hypoxic exposure.

Discussion. Gordon and Charipper(3) pointed out that there were definite erythropoietic effects following injection of gonadotropic hormones in rats. Their research showed that the adenohypophysis was not involved since androgens had positive effects even on hypophysectomized animals, while estrogens produced an intensification of the marrow hypoplasia of such animals. This experiment further indicates that gonadotropic changes occur at the same time that the animal has increased capacity to respond to hypoxia by production of ESF.

In measuring production of ESF by means of reticulocytosis, other stimuli that produce it must be ruled out. Radiation(4) and nerve stimulation(5) produce a degree of immediate mobilization of reticulocytes rather than the true physiologic response of ESF. Acapnia, resulting from the hyperventilation in an altitude experiment such as this, could be interpreted as the cause of erythropoietic activity. However, bone marrow activity also results when carbon dioxide tension is at normal and elevated levels(6). Grant and Root(7) have concluded that there is no demonstrable relation between erythropoietic activity and carbon dioxide tension.

Plum(8) has pointed out that reticulocytosis can be caused by injection of various chemicals and other causes, but these responses cannot be "considered pure in the same sense that other factors can be left completely out of consideration." In our experiment, since no extraneous factors were introduced, it was concluded that the reticulocytosis was due to the true physiologic stimulation of ESF.

Summary. These results indicate that ESF is produced in BDF1 mice after a 6-hour exposure to 22,000 feet. It is further demonstrated that these mice have augmented response to hypoxia at time of increased endocrine function at puberty.

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A Persistent Hog Cholera Viremia in Young Pigs.* (26214)

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When an attenuated hog cholera virus is given susceptible pigs, expectations are that a viremia will develop within 2 weeks after inoculation, followed shortly by clearance of virus from the blood as the pigs develop immunity. During epidemiological studies on hog cholera, some young pigs did not clear virus from their blood as expected. This persistent virus strain has been found to be cytopathogenic(1) in contrast to its ances-

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TABLE I. Influence of Age and Immune Status of Mother on Growth and Persistence of Hog Cholera Virus in Pigs.

Age	Status of mother	Growth results*	Presence of virus in blood 0 wk	1 wk	>3 wk
6 wk	Immune†	25/25	0/25	0/6	0/25
6 "	Non-immune	4/25	0/25	25/25	21/25
3 mo	" "	25/25	0/5	25/25	0/25

* Numerator indicates pigs that gained more than a pound daily or showed virus in blood. Denominator is No. of pigs tested.

† Six of these pigs came from non-immune mothers but were given colostrum from immune mothers.

tral virulent strain A maintained by serial passage in pigs and the derivative modified by rabbit passage(2) that produced this persistent strain, which were not. It seemed worthwhile to report this phenomenon of persistent viremia as well as characteristics found for the persistent virus.

Materials and methods. Litters of pigs were obtained from a disease-free herd maintained by the Institute. After weaning, 25 pigs 5 weeks of age and 25 pigs 11 weeks of age were placed in isolation and 1 week later, each was given 1 ml of a 10% spleen emulsion prepared from a rabbit infected with modified strain A hog cholera virus. From another herd, an additional group of 19 pigs whose mothers all had been immunized against hog cholera was inoculated in a similar manner at the age of 6 weeks. Also, 1 day prior to inoculation of virus, six 6-week-old pigs from the Institute herd were inoculated intraperitoneally with 125 ml of colostrum obtained from hog cholera immune mothers. Uninoculated pigs, 19 from the hog cholera immune herd and 6 from the disease-free herd, were kept as controls. For all of the pigs in these tests, temperatures were taken daily and weights were recorded each week. Results are presented in Table I.

Blood was taken from all pigs before inoculation and at weekly intervals thereafter and tested for presence of virus by inoculation into other susceptible pigs. Also, when they became moribund portions of spleen were removed from each, stored under dry-ice refrigeration, and later titrated for virus content. For comparison, after they became moribund, spleens were obtained from 5 pigs that had been inoculated with virulent hog cholera in the usual manner. Tenfold dilutions of spleen emulsion supernatants that ranged from 10^{-1} to 10^{-10} were prepared and pigs were inoculated to determine the greatest dilution that would produce hog cholera. Hog cholera was determined by clinical response and autopsy findings.

Results. Uninoculated pigs showed average daily gains of weight greater than 1.0 lb per day. Pigs inoculated when 3 months of age also showed average daily weight gains of greater than 1.0 lb daily when calculated over a period of 4 weeks, although weight gains, if any, during the second week after inoculation were slight. Inoculated pigs from immune mothers and those given colostrum from immune sows grew as well as uninoculated controls. In contrast, 21 of the 25 pigs from non-immune mothers that were inoculated when 6 weeks of age either gained less than 1.0 lb daily or showed no gain. Typical growth of the pigs is shown in Fig. 1.

After inoculation of virus, all pigs from non-immune mothers, whether 3 months or 6 weeks old, showed an elevated temperature that began 3 or 4 days after inoculation (Fig. 2). In all of the older pigs, as well as the few younger ones that grew well, temperatures remained elevated for 3 to 5 days, then returned to the normal range. In contrast, the younger pigs that failed to grow showed temperatures that ranged above 105°F for 3 to 5 days and then fell to a level around 104°F. They continued to eat, however, and showed normal activity until a few days before death, which occurred at various intervals from 6 to 17 weeks after inoculation. Only 3 of these 21 pigs that showed elevated temperatures and failed to grow during the first 4 weeks after inoculation appeared to recover. Their temperatures returned to normal range, virus disappeared from their blood, and they grew.

Modified virus was present in the blood of all pigs from non-immune mothers that were tested 1 week after inoculation. Tests 3 or 4 weeks after inoculation showed no virus in the blood of the older pigs or in the younger pigs that grew, but virus was recovered from the blood of pigs that failed to grow. This

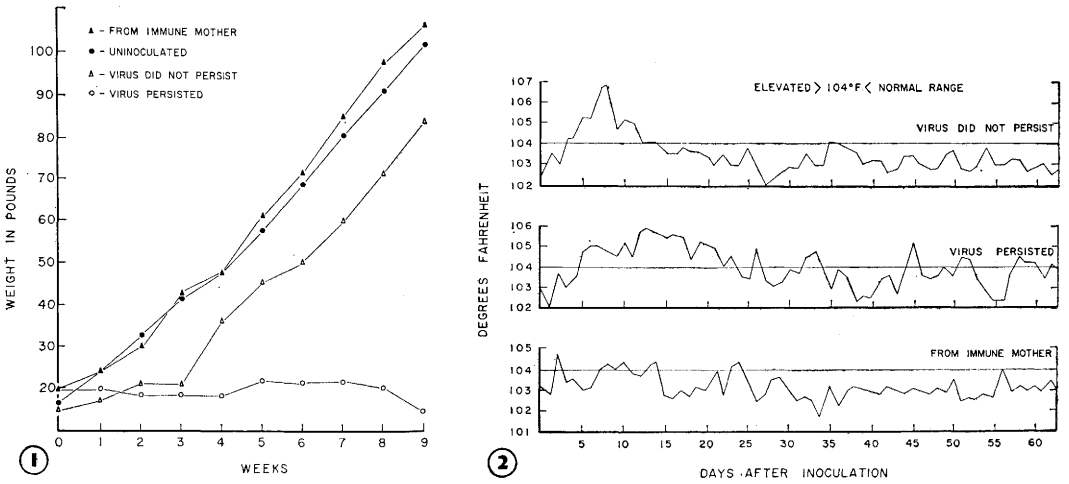

FIG. 1. Growth of pigs given hog cholera virus.
FIG. 2. Temperatures of pigs given hog cholera virus.

recovered virus had changed its character from modified to virulent. Additional pigs inoculated with this persistent virus, recovered from the spleen of stunted pigs, showed a shorter incubation period and died in less time than pigs given virulent virus maintained in the usual manner. Virus was not recovered either 1 week or 4 weeks after inoculation from the blood of pigs from immune mothers or those inoculated with colostrum.

As death approached in the stunted pigs, their temperatures occasionally rose abruptly to levels above 106°F and they developed paralysis of the hind limbs. After onset of these signs, pigs died within 2 or 3 days. Suspensions of spleen from 10 pigs with these signs infected susceptible pigs, 3 at a dilution of 10^{-7}, 3 at 10^{-8} and 4 at 10^{-9}. In contrast, spleen suspensions from 5 moribund pigs that had been inoculated with virulent virus in the usual manner infected 2 at a dilution of 10^{-4}, 3 at 10^{-5} and none at 10^{-6}.

Discussion. According to usual concepts, modified hog cholera virus should be present in the blood of a pig shortly after inoculation and then disappear after 2 to 3 weeks. When pigs 3 months of age or older were inoculated, usual expectations were met and virus was not demonstrated in the blood after 3 weeks. But younger pigs that were infected when 6 weeks of age generally failed to clear virus from their blood unless, either by suckling or by intraperitoneal inoculation, they received colostrum from mothers immune to hog cholera.

Viral persistence seems less complex if it is considered in relation to sites in which virus can localize after an initial attack. Viruses that persist are those types that localize in superficial tissues and, as a consequence, can be less affected by antibodies. A typical illustration is that of infectious canine hepatitis virus that initially produces viremia but, after antibodies develop, can no longer be demonstrated in the blood, but can be recovered and demonstrated for months afterward in the urine(3). Age of the dog apparently has little effect upon ability of this virus to persist. Viruses of the psittacosis-lymphogranuloma group, perhaps certain enteroviruses, and, of course, herpes virus all have their primary sites of multiplication in superficial tissues and such viruses have been found to persist for variable periods of time. Because fewer viruses produce persistent viremia, it has been suggested that in order to persist in blood a virus must be transmitted either to an unborn or to a newly born individual and reach accord with it without development of antibodies by the host(4). Such a condition of immunological tolerance has been described for lymphocytic choriomeningitis virus(5) transmitted *in utero* and seems to be the epidemiological method used by this virus to reach new hosts

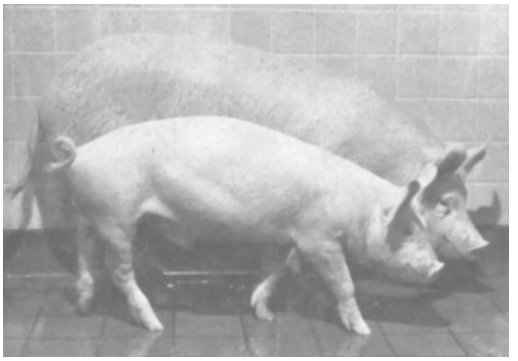

FIG. 3. These 2 pigs were littermates and were the same size when infected with hog cholera virus at 6 wk of age. Larger pig was given colostrum from immune swine while smaller was untreated. Smaller pig shows stunting effect produced by persistent virus.

(6). A similar immunological tolerance has been shown for pigs, but at an older age. Since hog cholera virus also transmits *in utero*(7), the ability to do so in combination with viral persistence may explain the obscure epidemiology of this virus.

Immunological tolerance of hog cholera virus by young pigs was characterized by their inability to overcome the virus, yet to survive and, except for stunting, appear active while tremendous quantities of virulent virus continued to circulate in their blood (Fig. 3). Virus which had persisted in this manner developed several interesting characteristics: (1) reversion to a greater virulence than that possessed by the ancestral strains, (2) ability to produce relatively enormous quantities in the blood, and (3) marked cytopathogenicity in tissue culture, a property not possessed by the ancestral strains. Either markedly enhanced or strikingly diminished pathogenicity is thought to be a mutation; it has been suggested that by appropriate control of environment, mutants can be selected (8). Under this definition, both the production and characteristics exhibited by this persistent hog cholera virus would seem to indicate that it is such a mutant, while the effects it produces in tissue culture would support this supposition.

Summary. A persistent hog cholera viremia was produced in pigs from non-immune mothers that were 6 weeks of age, but not in pigs that were 3 months of age or in pigs from immune mothers that were 6 weeks of age. Although a similar condition of immunological tolerance has been reported for other animals, it was produced either *in utero* or shortly after birth. These pigs, therefore, appear unusual because persistence of virus was established at an older age. Pigs with persistent viremia failed to grow and showed elevated temperatures but survived for periods from 6 to 17 weeks. During this interval, persistent virus reverted to a fully virulent state. When they became moribund, virus titers of spleens from stunted pigs ranged from 10^7 to 10^9 in contrast to 10^5 found in spleens from moribund pigs infected with virulent virus in the usual manner. The ability of hog cholera virus to transmit *in utero* and to persist in pigs after birth may have epidemiological implications.

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