NASA CONTRACTOR REPORT

NASA CR-441

NASA CR

CHRONIC ACCELERATION STUDIES-- PHYSIOLOGICAL RESPONSES TO ARTIFICIAL ALTERATIONS IN WEIGHT

by C. F. Kelly and A. H. Smith

NATIONAL AERONAUTICS AND SPACE ADMINISTRATION • WASHINGTON, D. C. • APRIL 1966

CHRONIC ACCELERATION STUDIES -- PHYSIOLOGICAL RESPONSES

TO ARTIFICIAL ALTERATIONS IN WEIGHT

By C. F. Kelly and A. H. Smith

Distribution of this report is provided in the interest of
information exchange.   Responsibility for the contents
resides in the author or organization that prepared it.

FINAL TECHNICAL REPORT

(1962 - 1965)

"CHRONIC ACCELERATION STUDIES -- PHYSIOLOGICAL RESPONSES TO
ARTIFICIAL ALTERATIONS IN WEIGHT."

Prepared by:

C. F. Kelly, Professor of Engineering

A. H. Smith, Professor of Physiology

BACKGROUND:

Accelerative forces are recognized by their tendency to change the
condition of rest or motion of affected objects. Forces and accelera-
tion are mutually defined in Newton's Laws of Motion: F = m x a. How-
ever, if a restrained body is exposed to an accelerative force, the
result is the phenomenon of weight, rather than an actual acceleration.
The relationship between weight, mass and accelerative force is derived
from Newton's Laws:

$$W = m\frac{a}{g}$$

Where: W is the weight (as lb., kg., etc.);

m is the mass (also as lb., kg., etc.);

a is the accelerative force (as dynes, ft/sec^2 etc.); and

g is the Earth's gravitation (in the same units as "a";

32 ft/sec^2; 980 dynes, etc.).

Thus, it is possible to change weight in two ways: naturally, by changing
the mass; and, artificially, by changing the accelerative force. Also,
the dynamic properties of various environments can be compared in terms
of the weight-to-mass ratio (the operational principle of accelerometers)
-- which is equivalent to the accelerative force in multiples of the
Earth's gravitation. It has become conventional to express the dynamic
aspects of the environment as "G" -- which being a ratio, is dimension-
less. There are no standard terms describing environmental conditions
with respect to accelerative force. We have called the prolonged expo-
sure to fields greater than Earth gravity: "chronic acceleration."
Although this terminology has limitations, it does seem to be readily
understood.

When the ambient accelerative force is altered moderately, any effect
on biological systems will result from the artificial change in weight.
Biological response to such changes can be anticipated on several
grounds. Some of these would be nonspecific, resembling the effects of
exercise. The work required for movement against an accelerative force
is proportional to the weight and distance moved. Within the Earth's

gravity this is expressed as:

Potential Energy = height x mass x gravitation

So, in a hyperdynamic environment, more work will be required for loco-
motion, maintenance of tonus, etc. However, any biological changes
resulting from this aspect of chronic acceleration should be similar
to those resulting from a greater degree of exercise under a lesser
accelerative force.

Other responses to changes in the ambient accelerative force will be
quite specific -- and the biological effects should not resemble those
of exercise or other natural activities. Some of these result from
changes in the specific weight (wt/vol). For example, in a 5G environ-
ment, the heart must handle a fluid with the normal specific weight of
iron. Other tubular organs with fluid contents, such as the gut,
would have similar problems. Organs with density gradients will be
particularly susceptible to changes in the environmental accelerative
force. An example of these is the brain, which has a lesser density
than the surrounding cerebrospinal fluid. As a result, the brain is
buoyant -- in humans at normal gravity with a buoyancy of 50 gms.
Brain buoyancy will be proportional to the ambient accelerative force --
it will be zero under conditions of weightlessness, 150 gms in a 3G
environment, etc. This buoyancy appears to be borne inelastically by
the brain, placing the tissue under a mechanical stress. The classical
work of Claude Bernard ("piqûre," 1848) and the metabolic sequellae in
some individuals recovering from brain concussion indicate a liklihood
of a general metabolic alteration from the application of mechanical
forces to at least some areas of the brain. Consequently, prolonged
changes in brain buoyancy may have important neuro-physiological
implications -- and especially the phenomenon of weightlessness, if the
normal brain buoyancy is a factor in its functional regulation.

In understanding the biological effects of chronic acceleration it
is important to distinguish between the specific and non-specific
phenomena. This can't be done with the experimental animals -- however,
it can be estimated by maintaining exercised as well as sedentary
controls. Such exercised controls will be particularly useful where
selection over several generations is involved.

Changes at the molecular level (i.e., molecular sedimentation, or
direct influence on thermochemical reaction) are not anticipated. The
forces involved in chronic acceleration are very weak compared to the
thermal energies ("Brownian" movement) of molecular and colloidal
particles. Any observed metabolic alterations will result from changes
in regulatory processes, and perhaps involving the endocrine system.

METHOD:

Gravity is the most constant and pervasive factor in our environment
-- and it is unique in that no way is known to interfere with or limit
it. Consequently, studies on Earth of the biological effects of accel-
erative forces will necessarily involve only "super-gravity" fields.
These conditions can be achieved in two ways: by changing the rate
of motion ("linear acceleration"); or by changing the direction

2

of motion (centrifugation). For long periods of time, only the latter
is feasible. If one maintained a field of 2.5G by linear acceleration
the object involved would go into an Earth orbit in 5.8 minutes, and
would escape the Earth's gravitation in 8.4 minutes (in 154 days
it would "attain" the speed of light!). Consequently, centrifugation
must be employed for producing long-term artificial changes in weight
(simulating a change in gravity). This procedure necessarily involves
turning, which also has a biological effect, as well as the production
of accelerative forces. However, this can be kept at a minimum by
elongating the centrifuge arms. Also, if the cages are "hinged",
the accelerative force, the resultant of the centrifugal force and
gravity, will be perpendicular to the cage floor. Changes in weight
produced by centrifugation are considered to be the same as those
produced by gravitation. Einstein's "Principle of Equivalence,"
states that the effects of accelerative forces are indistinguishable,
irrespective of their physical bases.

The objectives of this program include the development of apparatus,
techniques, and biological materials for the study of the effects of
chronic acceleration. The studies themselves are concerned with anatom-
ical, physiological, and pathological changes induced by the treatment
(i.e., soon after exposure to acceleration -- while the animals are
stressed), and also as involved in physiological adaptation and de-
adaptation (i.e., upon return to normal gravity, involving a sudden
loss of weight). These centrifugation experiments have been based,
generally, upon "before and after" treatment observations. At the
present understanding of the effects of chronic acceleration, such proced-
ures appear most productive of information. Such experiments last
several months to a year, with centrifugation stopped only a few
minutes a day for observation of the experimental animals. Most of
the experiments have been conducted with chickens, which are bipeds,
and posess a circulatory system more adaptable to the effects of chronic
acceleration than that of quadrupeds. Also, other environmental
experimentation (involving high altitude, thermal extremes, etc.) is
being carried out on this campus with chickens, which extends the
usefulness of the chronic acceleration experimentation.

The animal centrifuges, recently provided by a grant from NSF, and
designed by Mr. S. J. Sluka, are 18 feet in diameter, and "double-
decked" to carry 16 cages. The cages are arranged for the normal hus-
bandry of chickens. They have a total of 120 ft^2 floor space per cen-
trifuge, which will accomodate about 150 mature birds. However, the
cages can be readily modified to accomodate a larger animal (e.g., a
dog), or filled with smaller cages to accomodate rats, or other small
animals. One of the centrifuges has a mechanical drive with an opera-
tional capacity of 4.5G (considerably in excess of the tolerance of
kilogram-size animals, which is about 3G). The other centrifuge has a
hydraulic drive with an operational capacity of 6G -- approximately
the tolerance of rats. As of 1 July 1965, the mechanical drive has
logged 21,198,281 revolutions (equivalent to 491 days at 2.5G), and the
hydraulic drive 20,310,587 revolutions (equivalent to 470 days at 2.5G).
No major mechanical difficulties have been encountered with either machine.

RESULTS:
    Since the results of our experimentation have been described in some
detail in progress reports, they will be dealt with only in summary form.

3

The exposure of animals to chronic acceleration may result in a substantial mortality. For example, in a group of chickens introduced gradually to a field of 3G, only 70% may survive after three months. The pathology involved in this "chronic acceleration sickness" of chickens has been investigated and reported in detail by Dr. R. R. Burton. The debilities developed by birds in hyperdynamic environments are rather discrete, and two syndromes have been recognized. One involving leg paralysis is uniformly lethal, but the other may become spontaneously reversed, with the bird returning to a quasi-normal (asymptomatic) condition.

Both syndromes are readily reversed upon return to normal gravity, indicating that they do not depend on organic lesions. This indication is supported by a lack of specific lesions at autopsy. Also, when birds which have been taken-off the centrifuge, after becoming acceleration-sick, are returned to the greater accelerative force, there is not necessarily any recurrence.

Death from chronic acceleration sickness generally occurs in 3 or 4 days after the onset of symptoms. Simple inanition does not appear to be a factor, since acceleration adapted birds deprived of feed and water at 3G survive 6.3 ± 0.4 days (as compared with 12.8 ± 0.4 days at normal gravity), and die without exhibiting the typical signs of chronic acceleration sickness (Burton's Disease).

No qualitative differences in chronic acceleration sickness have been observed between acceleration-selected and unselected stocks -- the incidence is merely greater in the latter. Also, no qualitative difference in sickness is evident between the more susceptible (dying after a few days at 1.5G) or the more resistant (becoming sick and dying only after many months at 3G).

Survival in hyperdynamic environments requires physiological adaptation. A group of birds transferred rather gradually to a 3G environment may suffer a 30% mortality. However, if hatch-mates are introduced abruptly, all will die witin 72 hours. Adaptive changes may be induced by very low fields, ten days exposure to a 1.1G environment greatly reducing the mortality when subsequently exposed to greater accelerative force (e.g., 3G).

Physiological adaptation to hyperdynamic environments may be retained for long periods -- and perhaps indefinitely. Most physiological responses to chronic acceleration disappear in a relatively short time -- 3-5 weeks after return to normal gravity. However, adapted animals can be re-introduced to hyperdynamic environments 3-4 months later without apparent discomfort nor decrease in body size. From this it would appear that astronauts may be able to tolerate earth-gravity directly after fairly long periods of weightlessness. It also implies that very long periods of weightless exposure may be required before the full consequences (i.e., the gravity de-adapted state) become known.

The factors which permit animals to tolerate hyperdynamic environments are heritable. When unselected stocks of chicks are exposed to accelerative forces in the order of 3G, they will suffer a mortality of 6% per day. However, if survivors of such trials are reproduced serially

4

through five such selections the mortality rate is reduced to less than 1% per day. This is rather rapid selection progress, and geneticists consider that such a situation indicates a metabolic basis. Such selection also eliminates the disorientations and postural difficulties seen in some centrifuged birds upon return to normal gravity. (Conversely, reproducing birds showing these disorders approximately doubles their frequency.) However, this reduction in mortality at moderate acceleration is not accompanied by a great increase in the toleration limit (i.e., it remains at about 3G -- as for unselected stocks).

Among those tolerating chronic acceleration, one of the most characteristic responses is a repression of growth and development. Chickens raised in a 3G environment for several months may have a 40% reduction in body mass -- as compared to normal gravity controls. Upon return to normal gravity, some but not all of this difference will be made-up -- the degree of recovery being inversely proportional to the maturity at the time of return to normal gravity. It is interesing that in many experiments, the maximum growth is achieved at 1.5G, rather than at normal gravity.

Development, as indicated by the onset of sexual maturity, also is delayed in hyperdynamic environments. At 3G, sexual maturity in chickens required about 5 months, as compared to 4 months at normal gravity.

There also are anatomic responses to chronic acceleration -- however, these tend to be somewhat variable among experiments. Generally there is a decrease in the relative carcass quantity of "soft tissue" (material which can be separated mechanically from the skeleton) and an increase in relative quantity of skeleton and abdominal viscera (including the gastrointestinal tract). These changes resemble the effects of inanition, except that the latter treatment leads to a relative decrease in the G-I tract. In many instances, and especially those involving the centrifugation of young animals, the heart decreases in relative size. This is quite different from the effect of exercise, which generally leads to a 15-20% increase in heart size. However, this may be a species-specific response. In the chicken, the heart lies above the broad sternum, and is partly covered by the liver. When the acceleration starts at a young age (1-2 months), there is a tendency for a cavity to develop in the sternum, which is occupied by the heart.

Individual muscles may become hypertrophied -- up to 7-fold the relative size attained at normal gravity. However, this is a specific effect, occuring only in "anti-gravity" muscles, and not in the paired antagonist. This is different from the effect of exercise, where both muscles tend to hypertrophy. However, exercise is reciprocal, whereas postural maintenance in a hyperdynamic environment is not. Bones also become larger, but this is a "whole animal" effect -- increases in humerus size (non-load-bearing) equalling or exceeding those in the femur (load-bearing). This apparently is the "other-side" of the decalcification encountered in enforced bed rest, and in exposure to hypodynamic environments.

Changes also are evident in the blood. The concentration of plasma proteins increases, which may be necessary to regulate the distribution of water between blood and tissues with increased hydrostatic pressures.

5

Red cell numbers also increase, however the mean corpuscular volume decreases.

The chemical composition of tissues appears to be altered by chronic acceleration, but this has not yet been examined in detail. Generally, there is a significant increase in hydration, and a rather dramatic decrease in fat content. After long-term exposure to a 3G environment, depot fat may be virtually absent, and tissue fat only 15-25% of normal values.

Metabolic phenomena also appear to be affected by hyperdynamic environments. Preliminary observations indicate that the feed intake of male chickens is increased approximately 15% at 1.5G, and 36% at 2G. Consequently an exponential relationship appears to exist between feed intake and the ambient accelerative force:

$$F_G = F_M e^{kG} = 0.73 \ e^{.31G}$$

Where: F_G is the relative feed intake at a given accelerative force (i.e., relative to that at normal gravity, so when G = 1, F_G = 1);

F_M is the component of relative feed intake which is independent of weight -- i.e., it is mass dependent. Numerically this is 0.73 of the feed intake at normal gravity

k is the proportionality constant, relating relative feed intake and accelerative force, which has the value 0.31.

G is the accelerative force in multiples of the Earth's gravitation.

Assuming that this relationship would apply over a range of 0-3G, the energy requirements for environments with varying dynamicity can be estimated. For example, to furnish a caloric intake equivalent to 3000 kcal per day on Earth, the following would be required under other dynamic conditions:

Weightless	(0G)	2190 kcal/day
Moon	(0.18G)	2310 "
Marrs	(0.38G)	2460 "
Earth	(1.00G)	3000 "
Neptune	(1.53G)	3570 "
Jupiter	(2.65G)	5000 kcal/day

There also is evidence of qualitative change in metabolic function, as indicated by the incapability of birds raised under moderate acceleration fields to form much fat. This is not a simple matter of feed restriction, since feed intake is well within their feed capacity -- e.g., their feed intake may be doubled at low temperatures.

There also are indications that the biological response to a change in the ambient accelerative force can be altered therapeutically. Under chronic acceleration, drugs which limit sympathetic accomodation (e.g., Reserpine) approximately double the mortality rate. Androgen

6

treatment of females increases their mortality, but only to the greater rates usually encountered with males. Other materials (vitamin supplementation, glucosteroid, cortisone, ACTH, and estrogen treatment of males) are without any marked or noticeable effect. Thyroid stimulating hormone (TSH) is quite protective, practically eliminating mortality in centrifuging birds. However, thiouracil treatment, which limits thyroid function, does not have a reverse effect.

CONCLUSIONS:

From these results, and those of others, it is apparent that living things can become physiologically adapted to chronic acceleration -- up to some limiting intensity, which is inversely related to body size. Thus, individuals have capacities to tolerate environmental variation not previously experienced by them or their ancestors. Whether this tolerance involves the establishment of new physiological processes, or merely a recombination of adaptive processes developed to meet other stressors, will require much more study to resolve. It is interesting that the rate at which such adaptation is acquired in chickens is similar for that to high altitude -- and much slower than that to high temperature.

Over the tolerable range, the physiological and anatomical changes appear to be proportional to the accelerative force -- although neither the nature of the changes (increase or decrease) nor the kinetic relationships (rectilinear, exponential, hyperbolic, etc.) are uniform. However, the response to accelerative forces can be described mathematically. From such equations, the physiological effects of gravity can be estimated, and those of prolonged weightlessness can be predicted. However, prediction and actuality must not be confused. Such predictions must be tested in actual weightlessness -- and logically, such predictions should be the basis for designing satellite experiments. If the predictions of chronic acceleration are valid, then this technique furnishes a relatively convenient means of developing information pertinent to bioastronautics.

Differences between the biological effects of weightlessness and the predictions from chronic acceleration studies will occur only if there are different and discontinuous regulatory processes for environments above and below normal gravity. Since, physically, Earth gravity is not a critical point (i.e., it is not zero), such a situation appears unlikely. However, even if major deviations exist between predicted and observed weightlessness effects, knowledge of the responses of animals to hyperdynamic environments is quite important. If all of our information on the biological effects of accelerative forces is limited to two points (weightlessness and Earth gravity) few generalities will result.

PUBLICATIONS:

The effect of body weight on joint and skin disorders of domestic birds.
C. M. Winget, A. H. Smith and C. F. Kelly. Poultry Sci. 57, 1253-54
(1958).

Physiological effects of artificial alterations in weight. A. H. Smith,
C. M. Winget and C. F. Kelly. Naval Research Rev. pp 16-24
(April, 1959).

Growth and survival of birds under chronic acceleration. A. H. Smith,
C. M. Winget and C. F. Kelly. Growth. 23, 97-108 (1959).

An animal centrifuge for prolonged operation. C. F. Kelly, A. H. Smith
and C. M. Winget. J. Appl. Physiol. 15, 753-57 (1960).

Physiological hypertrophy of avian muscle. T. A. Holliday and A. H. Smith.
Anat. Rec. 139, 239 (1961)

Adaptation of birds of chronic acceleration. A. H. Smith and C. F. Kelly.
Physiologist. 4, 111 (1961).

Quantitative measurement of labyrinthine function in the fowl by nystagmography.
C. M. Winget and A. H. Smith. J. Appl. Physiol. 17, 712-18 (1962).

Effects of chronic acceleration on induced nystagmus in the fowl.
C. M. Winget, A. H. Smith and C. F. Kelly. J. Appl. Physiol. 17,
709-11 (1962).

Use of available space in rocket flights for biological research. S. Goren,
and E. L. Besch. Pac. Missile Range Tech. Memo. PMR-TM-63-2.

Pathology of chronic acceleration. R. R. Burton, W. P. C. Richards, and
A. H. Smith. Aerospace Med. 34, 249 (1963).

Influence of chronic acceleration upon growth and body composition. A. H. Smith
and C. F. Kelly. Ann. N. Y. Acad. Sci., 110, 410-24 (1963).

Chronic acceleration sickness. R. R. Burton, and A. H. Smith. Aerospace
Med. 36, 39-44 (1965).

Effect of accelerative forces on avian embryogenesis. E. L. Besch,
A. H. Smith and S. Goren. J. Appl. Physiol. (in press).

Morphological changes in avian eggs subjected to accelerative force.
E. L. Besch, A. H. Smith and M. W. Walker, J. Appl. Physiol. (in press).

A hydraulic pressure tester of egg shell strength. S. J. Sluka, E. L. Besch
and A. H. Smith. Poultry Sci. (in press).

Biological effects of chronic acceleration. A. H. Smith and C. F. Kelly.
Naval Research Rev. (in press).

Orientation in systems with asymmetric density distribution. S. J. Sluka,
A. H. Smith and E. L. Besch. (in manuscript, submitted to the
Biophysical Journal).