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

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

Prepared under Purchase Request R-53 to Office of Naval Research *by*
UNIVERSITY OF CALIFORNIA
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"CHRONIC ACCELERATION STUDIES -- PHYSIOLOGICAL RESPONSES TO ARTIFICIAL ALTERATIONS IN WEIGHT."

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BACKGROUND:

Accelerative forces are recognized by their tendency to change the condition of rest or motion of affected objects. Forces and acceleration are mutually defined in Newton's Laws of Motion: $F = m \times a$. However, 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 dimensionless. There are no standard terms describing environmental conditions with respect to accelerative force. We have called the prolonged exposure 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 locomotion, 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 environment, 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 accelerative 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

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 anatomical, 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 procedures 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 husbandry of chickens. They have a total of 120 ft^2 floor space per centrifuge, 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 operational 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.

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 $\pm$ 0.4 days (as compared with 12.8 $\pm$ 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

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.

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

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.

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