The described procedure is simple, inexpensive and reproducible. It can be used to explore not only the duration of action of ethanol but also the modification of activity of ethanol by other drugs. Our data indicate that the order of potentiating properties of the drugs used were reserpine >, chlorpromazine >, phenaglycodol >, meprobamate >, hydroxyzine >, morphine >, *d*-propoxyphene and codeine. The latter two drugs failed to potentiate ethanol-narcosis.

Studies of the possible potentiating action of tranquilizers and other drugs on alcohol depression is becoming increasingly important because of the increase in therapeutic usage of tranquilizers and continued social usage of alcohol.

*Zusammenfassung.* Eine Methode zur Messung der Potenzierung von Tranquilizern und Analgetika auf Äthanoldepression wird beschrieben. Unbeweglichkeit von Mäusen wird als Kriterium der Depression genommen. Die fünf Tranquilizer, die gebraucht wurden, haben Äthanol in verschiedenen Graden potenziert. Von den drei analgetischen Drogen hat Morphin, nicht aber *d*-Propoxyphen und Codein, Äthanolnarkose potenziert.

R. B. FORNEY, H. R. HULPIEU, and F. W. HUGHES

*Department of Pharmacology, Indiana University School of Medicine, Indianapolis (U.S.A.), July 2, 1962.*

## PRO EXPERIMENTIS

### Zunahme der tödlichen Dosis von g-Strophanthin beim Meerschweinchen in Abhängigkeit von der infundierten Flüssigkeitsmenge

Bei Meerschweinchen in Urethannarkose wurde die tödliche Dosis von g-Strophanthin durch Dauerinfusion mit Geschwindigkeiten von 10 und 1,5 µg/kg/min bestimmt. Dabei wurde die Konzentration der Lösungen und dementsprechend die infundierten ml/min so verändert, dass die letale Menge bei beiden Geschwindigkeiten einmal in 2 ml, zum anderen in rund 15 ml/Tier enthalten war. In der Tabelle sind die geometrischen Mittelwerte aus Versuchen an je 6 Tieren zusammengefasst. Die mittlere tödliche Dosis war unabhängig von der Infusionsdauer, stieg aber in Abhängigkeit von der infundierten Flüssigkeitsmenge um rund 20% an.

In der Literatur ist wiederholt ein Anstieg der tödlichen Dosis von g-Strophanthin bei Verlängerung der Infusions*dauer* über 30 min hinaus beschrieben worden (FROMHERZ und BÄCHTHOLD[1]; HOFFMANN und LENDLE[2]; KRAUPP, OBENAUS, PILLAT und STUMPF[3]). Es ist wahrscheinlich, wenn auch nicht mehr im einzelnen nachprüfbar, dass bei einer Versuchsdauer von mehr als 2 h grössere Flüssigkeitsmengen gegeben wurden und der Anstieg des Titers hierauf und nicht auf eine Elimination von g-Strophanthin zurückzuführen ist. Da Meerschweinchen in Urethannarkose kaum Harn absondern, kommt eine Ausscheidung durch die Nieren nicht in Frage. Wahrscheinlich wird das g-Strophanthin zusammen mit der infundierten Flüssigkeit in der Peripherie abgelagert.

Die praktische Konsequenz aus diesen Ergebnissen ist offensichtlich. Auf eine theoretische Folgerung soll aber noch hingewiesen werden: Wenn sich im akuten Versuch nicht einmal die Elimination des kurz wirkenden g-Strophanthins einwandfrei feststellen lässt, so ist das bei kumulierenden Glykosiden erst recht aussichtslos.

Tödliche Dosen von g-Strophanthin bei Dauerinfusion unter verschiedenen Versuchsbedingungen

| g-Strophanthin, µg/kg/min | 10 | 1,5 | 10 | 1,5 |
|---|---|---|---|---|
| Verbrauchte ml/Tier | 2,0 | 2,0 | 14,5 | >16,0 |
| Infusionsdauer, min | 12 | 131 | 25 | >160[a] |
| Mittlere tödliche Dosis, µg/kg | 196 (185–208) | 196 (186–207) | 244 (221–269) | >235 (213–259) |

[a] 2 Tiere überlebten länger als 200 min.

*Summary.* The $LD_{50}$ of ouabain in guinea-pigs rose in correlation with the infused volume but not with increasing duration of infusion.

W. SCHAUMANN

*Pharmakologisches Laboratorium der Fa. C. F. Boehringer & Söhne GmbH, Mannheim-Waldhof (Deutschland), 3. Juli 1962.*

[1] K. FROMHERZ und H. P. BÄCHTOLD, Helv. physiol. pharmacol. Acta *8*, 454 (1950).

[2] G. HOFFMANN und L. LENDLE, Arch. exp. Path. Pharmak. *212*, 376 (1951).

[3] O. KRAUPP, H. OBENAUS, B. PILLAT und CH. STUMPF, Arch. exp. Path. Pharmak. *237*, 388 (1959).

## CONGRESSUS

### France

### Symposium of the European Biology Section of the International Association of Gerontology

Paris, April 2–4, 1962

The symposium was held at the Department of Physiology of the Faculté de Médecine and attended by 42 research workers actively engaged in basic research on the ageing processes.

The various original contributions presented to this meeting will later be published in full in various journals and in their original language, but it has been felt that a comprehensive English summary of the various papers might be useful both for experimental gerontologists and for biologists interested in the modern trends of research on ageing.

Three main topics were discussed in this meeting: (1) The phenomenon of 'differential ageing' in Man; (2) Biochemistry of ageing; and (3) The action of some external factors on the rate of ageing. The discussion leaders for these three main themes were, respectively, Professor F. BOURLIÈRE (Paris), Professor F. VERZÁR (Basel) and Dr. P. ALEXANDER (London). A final session, devoted to various specific problems was chaired by Dr. T. GEIL (Kjobenhavn).

The summaries herewith published (and prepared by the authors) have been grouped in the order of presentation of the original papers. Where known, the title of the journal in which the full articles will be published has been mentioned.

F. Bourlière

## Theme 1. Differential Ageing in Man

*Ageing in Two Caucasian Populations Living in Very Different Ecological Conditions*

In order to appreciate the role of very different environmental conditions on the rate of ageing of various morphological, physiological and biochemical characteristics in clinically healthy white males, 246 urbanized Parisians and 346 rural Kabyles living in their traditional way in Algerian mountains, have been studied by the same investigators, using the same methods and even the same apparatuses. All subjects have been taken at random in their respective populations. — A similar pattern of age changes in the two populations has been found for stature, thorax morphology and blood pressure, although Parisians and Kabyles differ in their average values for every age-class. — Age changes in weight, subcutaneous fat deposits, serum cholesterol and $\beta$-lipoproteins are, on the contrary, very different in urbanized Parisians and in rural Kabyles. Such differences are, at least partly, due to the differences in diet.

The paper has been published in the 'Revue Francaise d'Études Cliniques et Biologiques', *7*, 629 (1962).

F. Bourlière and S. Parot (Paris)

*Age Changes in Japanese and Frenchmen; a Comparative Study*

The same pattern of age-changes is found in Japanese and Frenchmen for the following morphological and physiological characteristics: stature, basal metabolic rate, vital capacity, maximum breathing capacity, strength of grip, blood pressure and urinary 17-ketosteroids. Contrary to what happens in West-Europeans, Japanese do not fatten between the ages of 25 and 65 and their blood cholesterol (at least in males) does not show any regular increase during the same period. Despite their stature and weight, which are inferior to those of Frenchmen in any age-group, Japanese have average values for basal metabolic rate, strength of hand grip and output of 17-ketosteroids which are closely similar to those of Western Europeans. This fact may be due to a relatively more important protoplasmic mass and a smaller amount of fat deposits.

This paper will be published in the 'Revue Française de Gérontologie', vol. 8 (1962).

T. Nakayama (Tokyo) and F. Bourlière (Paris)

*The Influence of the Socio-Economic Level in the Ageing Pattern of the French Population*

96 matched pairs of clinically healthy old Parisians of both sexes and similar ages, but belonging to different socio-economic groups ('very high' and 'medium'), have been studied. Statistically significant differences (in favour of the higher socio-economic level) have been found in Intellectual Quotient, Vocabulary, Intellectual Efficiency, Memory, Stature, Vital Capacity and Strength of the hand grip. On the contrary, the basal metabolic rate and the blood cholesterol are consistently lower in individuals of lower socio-economic level.

F. Clément (Paris)

*Is Mental Ageing Accelerated in People with Cerebrovascular Family Histories?*

Two groups of clinically healthy people of the same age and socio-economic level have been compared, one in which one at least of the ascendants (mother or father) or collaterals (brother or sister) died from obvious cerebrovascular disease, and one in which ascendants and collaterals died from other causes. The main results are summarized in the following Table.

| | Men | | Women | |
|---|---|---|---|---|
| | People with cerebro vascular disease in their family history | Controls | People with cerebro vascular disease in their family history | Controls |
| Numbers | 27 | 41 | 17 | 36 |
| Age | 70.3 | 70.5 | 67.8 | 68.9 |
| Cultural level | 4.82 | 4.73 | 4.41 | 4.31 |
| Intellectual Quotient | 124.0 | 124.0 | 121.0 | 122.0 |
| Visual retention test | 5.79 | 6.85 | 5.82 | 5.86 |
| Wechsler memory scale | 28.92 | 32.48 | 34.16 | 33.15 |
| Coding test | 53.40 | 56.28 | 55.47 | 55.20 |
| Systolic blood pressure (mm Hg) | 16.1 | 15.2 | 15.6 | 15.2 |
| Weight (kg) | 66.2 | 69.7 | 61.0 | 59.9 |
| Total cholesterol (g/l) | 2.62 | 2.62 | 2.87 | 2.85 |
| $\beta$-Lipoproteins (g/l) | 4.35 | 4.50 | 4.76 | 4.62 |

It can be seen that *in males*, normal people with cerebro-vascular family history have always lower performances than controls for the visual retention test, the Wechsler memory scale and the coding test. For the first two tests, the differences between the two groups are statistically significant at the level of $P = 0.01$. People with cerebro-vascular family history also tend to have a higher systolic blood pressure than the controls, when no such difference exists for blood cholesterol and $\beta$-lipoproteins.

Among females, a cerebro-vascular family history has apparently no such accelerating effect on the rate of decline of the mental abilities tested.

This paper has been published in 'La Presse Médicale' *70*, 1637 (1962).

F. Bourlière and J. Poitrenaud (Paris)

*Analysis of Behavioral Changes Associated with Age in Healthy Adults*

Recent research from these laboratories has shown an interesting constellation of age changes of a psychological and physiological nature in relatively healthy adults, results which may prove of considerable significance both from theoretical and practical points of view. In a previous study it was found that blood pressure, within normal ranges, was correlated with psychomotor speed in men over the age of 65 years. In related work on young and old adults it was found that psychomotor speed tended to have the properties of a general psychological factor in the aged, i.e., many seemingly different kinds of behavior were slowed. The results suggested that it was desirable to determine if the general speed factor, which seems to emerge with advancing age, is related to other measured physiological characteristics. To this end a collaborative study was undertaken between the National Institutes of Health and the Federal Aviation Agency. The research is continuing and the present report is based upon the analysis of the results obtained from the first 160 men between the ages of 23 and 69 years. These men were active civil air pilots and air traffic controllers. Each man received a physical examination as well as psychological and clinical laboratory tests. Of interest here are the correlations with chronological age and the intercorrelations of the measurements. A total of 33 variables were intercorrelated. These included the 15 different psychomotor speed measurements with the Psychomet, the Trail Marking Test, Block Design, Vocabulary and Digit Symbol Tests of the WAIS, blood pressure, pulse rate resting and after exercise, fasting blood sugar and blood cholesterol level. Of 32 possible correlations with chronological age, 28 were significant at the 1% level. The correlations of psychological measurements with

chronological age were higher than the physiological measurements, e.g., 0.59 for the Psychomet and 0.42 for the Digit Symbol test; whereas it was 0.28 for diastolic blood pressure and 0.25 for cholesterol level.

The pattern of results makes it difficult to accept the hypothesis that age changes in measured vascular functions lead to the decrement in psychomotor reactivity with age. However, both the psychological and the physiological changes may be a joint manifestation of altered control by the central nervous system; such alterations being manifested earlier in complex psychological and psychomotor functions.

J. E. BIRREN and W. SPIETH

*Channel-Capacity, Activation and Age*

This paper examines the application to ageing studies of two lines of theory which have become prominent in psychology during recent years: firstly the concept of the brain as a communication channel of limited capacity in which signals may be disturbed by random neural activity ('neural noise'); secondly the relation between arousal or activation and cortical efficiency. Both lines have implications regarding sensory thresholds and speed of performance.

Work showing raised differential thresholds among older people indicates that these are not due to attenuation of signal in the sense organs but to either decreased channel-capacity or to increased randomness of neural activity in the central pathways and brain or, more probably, to both. Some suggestions about the sources of increased neural noise in old age are surveyed.

Studies not concerned with ageing have shown that moderate levels of activation or arousal improve performance and lower sensory thresholds, while very high levels lead to impairment. It is normally assumed that older people are liable to suffer from under-activation, but there are reasons to suppose that in some cases age changes might be due to over-activation leading to loss of channel-capacity and higher neural noise levels.

A. T. WELFORD (Cambridge)

*The Liverpool Age Project: Preliminary Communication on Population and Methodology*

This project involves a detailed study of 600 adult subjects, drawn from the local population in the city and environs of Liverpool (England). The total number consists of 12 groups of 50 subjects each, in respect of each sex in the 6 age-groups 20–29 to 70–79 inclusive. Within each age/sex group there is a close approximation to national distributions for socio-economic classification and, for the project as a whole, good coverage of the principal occupational groupings as used by the Census.

Each subject takes part in two examinations, each lasting about 2 h. The first of these was a group procedure, during which the following data were obtained: (1) Biographical information — including educational and occupational history, marital status, number of children, length of residence in north-west England, and number and nature of leisure interests. (2) List of reported serious illnesses or injuries. (3) Tests of non-verbal intelligence, of vocabulary and of personality.

During the second occasion, each subject is examined individually, spending about 30 min in each of four rooms. The following information is obtained: (1) Sitting and standing height. (2) Weight. (3) Timed expiratory volume (1.0 sec). (4) Index of body-build. (5) Blood pressure. (6) Strength of grip. (7) Persistence of grip, at two-thirds maximum. (8) Respiratory questionnaire (including smoking habits). (9) Sleep habits questionnaire (including peak and trough of daytime alertness, and use made of sleeping tablets). (10) Auditory acuity. (11) Visual acuity (Landolt) for stationary and moving test-object. (12) Tests being investigated as measures of functional efficiency of the brain: (a) Digit span, to auditory and visual presentation. (b) Letter-to-digit coding, natural pace and also speeded. (c) Persistence of after-effects to rotating spiral. (d) Memory for designs. (e) Mazes. (f) Trail-making task.

The barometric pressure, temperature and relative humidity are recorded at the time of examination, and the pulse rate is noted on 9 occasions — on entering and leaving each room and also before reading the blood pressure.

The examinations are scheduled to be completed by the end of July, 1962, and the main results of the statistical analyses should become available by the summer of 1963. Collateral information will by then also be available about selected groups of subjects who have participated in the experimental projects of Unit members: topics under study include reaction-time, flicker fusion frequency, immediate memory, confidence and problem solving.

A. Heron (Liverpool)

*Results of a Simple Memory Test in Various Groups of Old People*

A simple memory test formed part of two extensive surveys on the health of the aged. One study took place in 3000 persons of 65 years and older, in a city (Groningen) in the North of the Netherlands, the other survey, under the auspices of the Organization for Health Research T.N.O., performed by nearly 400 general practitioners, in more than 3000 aged persons among the Dutch population over 65 years of age. The aged had been divided into 8 groups according to age, and sex; each group was a random sample in itself. The memory test consisted of a number of items from the Wechsler Memory Scale, which had been partly modified and simplified.

The results of the two surveys, with respect to both the individual items and the complete test, could be compared for a number of data; they appeared to differ generally only slightly. This was true e.g. for the finding that in each age group significantly more men than women obtained good results; the older the age-group, the less people could manage the test. In particular after the age of 80 the decline was remarkable.

Good objective or subjective health often went together with obtaining an appreciable number of points. In the highest income class, more old people got good results than in the other income classes, according to the T.N.O. survey. In the Groningen survey more aged persons in the higher social classes did well than in the lower social classes.

Several more results of combinations of the outcome of the memory test with a few other variables, such as retirement, are reported as well.

R. J. VAN ZONNEVELD (The Hague)

*Some Observations on the Process of Ageing, at an Advanced Age, for Certain Psychological Functions*

The aim of this research was to determine whether, in a year's time, some mental, intellectual or psychomotor functions of old persons had undergone modifications.

The sample was composed of 21 old persons aged 64 to 81, most of them being situated between 70 and 79 years of age. All these subjects were of a very modest socio-economic level and of a rather low cultural level.

We adopted the longitudinal method for our study: the same tests-battery was applied twice; each of the 21 subjects was examined after a precise interval of one year. None of the subjects who were part of the study suffered from any serious impairment during that one year interval, nor were given any medical treatment which might have disturbed the results in the tests.

Besides this, we had a comparison sample at our disposal, composed of 65 subjects, aged 64 to 86, who served to standardize our tests. For each test we calculated: (1) the arithmetic mean (2) the standard deviation ($\sigma$).

We have thus been able to determine for each of the 21 subjects studied: (1) his performance, for each test, *in the course of the first examination* he underwent. To do so, we calculated the deviation between his own result in the test and the arithmetic mean obtained in the same test by the reference-group (i.e. the 65 subjects having served for the standardizing of old people). This deviation was expressed in tetrons[1]. (2) In the same way, his performance, for each test, *in the course of the second examination.*

The difference between the two tetrons (test and retest ones) are thus expressing, for each subject and for the tested function, either

[1] 1 tetron = $^1/_4$ of the standard deviation = $\sigma/4$.

his stability or his decline, or maybe his improvement[2], after one year has elapsed.

*The results.* (a) It is only in very rare cases[3] that the modification observed in the individual performances reaches 4 tetrons, that is $1\sigma$, and this whatever the direction of the modification may be, whether towards decline or amelioration. In most of the cases the differences range about 1 or 2 tetrons.

Therefore, *individual modifications* are non-significant and remain in the normal limits of the fluctuation around the initial value obtained by each subject in each test. Consequently, it can be ascertained that, in spite of his old age, no subject has changed much in the lapse of one year.

(b) Nevertheless, we wished to know whether a *general tendency in the group*, either towards decline or towards amelioration, did not appear for certain functions. To that end, we calculated the 't' of Student for each test, taking into account, on the one hand, all the non-significant cases of falls in the performances and, on the other, all the non-significant cases of amelioration in the performances[4].

None of the 't' calculated proved significant. Consequently, no tendency to decline (or to improvement) can be observed for this very aged persons group, in the lapse of one year, for any of the tested functions[5].

(c) We also calculated Spearman's 'rho' between the ranks held by the 21 subjects in the test and their ranks in the re-test. The correlation coefficients prove to be very high for all the functions tested, both intellectual and mental ones as also psychomotor ones. These coefficients lay between 0.64 and 0.93.

So the *reliability of our instruments* of measure is very high, which assigns still more weight to the above experimental data.

D. Durey and S. Pacaud (Paris)

## Theme 2. Biochemistry of Ageing

### *Role of Free Radicals in Ageing*

Ageing, cancers (at least some), and mutation are attributed basically to the side effects of endogenously formed free radicals.

If free radicals do contribute to ageing, then raising the concentration in the organism of compounds which react rapidly with free radicals might slow the ageing process. The first experiment based on this possibility employed AKR (male) and C3H (female) mice. After weaning groups were placed on powdered diets (*ad libitum*) containing no additive or the hydrochloride of an antioxidant. AKR mice: cysteine (1% w), 2-mercaptoethylamine (1% w), and 2,2-diaminodiethyl disulfide (0.5% w), prolonged the half-survival time (HST) (age at which 50% are dead) from 8 months (controls) to 10 months — 25% prolongation ($p < 0.01$). C3H mice: no certain effect noted. The second experiment utilized Swiss mice (males) in addition to the above strains. Pelleted food was used in hope of achieving longer elevated tissue levels of the additives (1% w). 2-Mercaptoethylamine prolonged the HST of C3H mice from 14.5 to 18.3 months — 26% increase ($p < 0.01$); hydroxylamine increased HST slightly — 7%. Cysteine and hydroxylamine (2% w) increased the HST of AKR mice by 15%. Swiss mice: no prolongation.

In the first of two current experiments the following compounds are being evaluated at $^1/_4$% w in powdered diets in groups of Swiss (male), C3H (female) and AKR (male) mice: 2,5-di-tert-butylhydroquinone, butylated hydroxyltoluene, propyl gallate, A.E.T. (2-aminoethyl isothiouronium bromide), and hydroxylamine hydrochloride (this compound at $^1/_2$% w). The HST's for these compounds in the Swiss mice, given in the above order, are $>17$ (at 17 months of age 61.6% of this group was still alive), 15.0, 15.0, 15.5, and 14.0 months, respectively, while the value for the control group was 15.0. 2,5-Di-tert-butylhydroquinone is the first compound found that prolongs the HST of Swiss mice. Corresponding figures for the C3H mice are 14.0, 14.5, 14.5, 13.5, and 17.0 months respectively; control groups — 15.5 months. 2,5-Di-tert-butylhydroquinone, butylated hydroxytoluene and propyl gallate increased the gross tumor incidence in both C3H and Swiss mice. For example, at 17 months of age 25% of the control C3H mice had tumors while the corresponding figure for the group on 2,5-di-tert-butylhydroquinone was 52%. None of these compounds prolonged the HST of AKR mice.

AKR (male) mice are being employed for the second of the current experiments. At 9 months of age the % surviving in each group is: —56.0; alkylated thiobis-phenol ($^1/_4$% w)—83.0; Vitamin diet fortification mixture (Nutritional Biochemical Corp.) (2% w)—75.0; thioglycolanidide ($^1/_4$%)—73.0; and thioglycol-0-anisidide ($^1/_4$%)—60.0.

These results are encouraging and provide some support for the concept that endogenously produced free radicals contribute to the ageing process.

D. Harman (Nebraska)

### *Ageing of Newly Formed Collagen*

During the natural process of ageing of collagen in the body, the inter-chain bonds are known to increase. When collagen fibers from tendons or from the corium of skin are heated, these bonds are broken at temperatures above 58°C[6].

A period of 10 min at a temperature of 65°C can be used as a practical method for differentiating between the behaviour of young and of old collagen. The quantity of oxyproline complexes which goes into solution has been found to be large in young and small in old, in the corium from human skin, cattle hide[7], and also in tendon fibres from the tail of the rat[8] and tendons of the frog[9].

In *human skin* the changes are very marked up to puberty, and then become less through adult life, but are quite obvious by the time senility is reached. Figure 1 shows these changes with age.

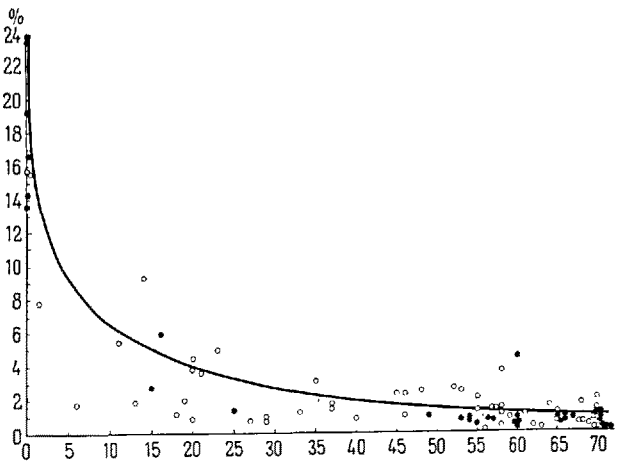



Fig. 1. Percentage oxyprolin liberated at 65°C in 10 min. • cases published in[10]; • new cases.

Using the method of oxyproline estimation[5] we have shown with Willenegger that, in wound healing, the newly formed collagen of the scar tissue is *young* collagen at every age of the host, and then ages in the usual way. Thus a one-year-old scar in a 50-years-old individual contains collagen which has the characteristics of a one-year-old child. After about 10–15 years, this scar collagen is found to have aged and is now almost similar to the rest of the body collagen (Figure 2).

This finding is of a certain basic significance in view of the rather generally accepted opinion as to the nature of the ageing of 'protoplasm'.

[2] The latter could as well be considered as due to learning.
[3] One or two cases by test.
[4] Besides, we already saw, in the preceding paragraph, that significant modifications were very rare.
[5] This may be due to the fact that the performances are already very much diminished in that aged group compared to those of younger groups such as adults from 40 to 44.
[6] F. Verzár, Helv. physiol. Acta *13*, C 64 (1955).
[7] F. Verzár, Gerontologia *4*, 104 (1960).
[8] F. Verzár and A. Mayer, Gerontologia *5*, 163 (1961).
[9] J. Brocas and F. Verzár, Gerontologia *5*, 228 (1961).
[10] F. Verzár and H. Willenegger, Schweiz. Med. Wschr. *91*, 1234 (1961).

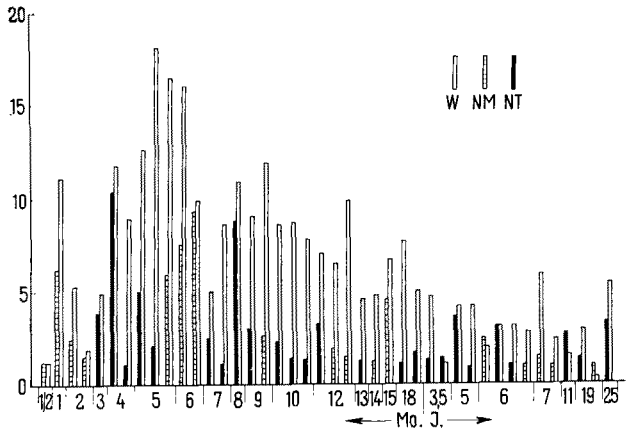



Fig. 2. Percentage oxyprolin liberated from scar tissue (white columns), from normal skin of the same person (black) and from normal values of persons of the same age (gray). W, wound; NM, normal middle value; NT, normal tested on the same person.

LANSING[11], writing on 'General Biology of Senescence' in Birren's *Handbook of Ageing* in 1959, states (pp. 130–131), after discussing theories of ageing based on the ageing of colloids: 'The fact is that there is one fundamental difference between living cells and machines . . . . or colloids . . . Protoplasm is in a perpetual state of flux; there is a constant turnover of its constituents and replacement of individual molecules. *The colloids in old protoplasm are new colloids but different from those of the young; . . . . The old organism does not contain old colloids; it contains "newly" formed colloids of an old character*'.

The contrary is however true for collagen, which constitutes about half of the body protein.

Collagen ages because, after it is deposited, it has no turnover; thus in an old person collagen *is* 'old'. Our observation shows, however, that the newly formed scar-collagen is *young* collagen, also in an old person.

While it is not permissible to generalize, it should be realized that other newly formed proteins probably also have a 'young' pattern in the aged.

In 'definitely postmitotic cells' as cells of the nervous system DNA may age also since it has no turnover, being without mitosis. Since it is the essential factor for initiating protein and enzyme production in the cell, this will be disturbed and a disintegration of the cell will follow, as in ganglionic nerve cells.

The possibility has been discussed that in 'fixed postmitotic cells', which only occasionally undergo mitosis, 'partly' aged DNA may induce an 'aged pattern' of proteins and enzymes in newly formed protoplasm, which may explain the special nature of ageing of erythroblasts and erythrocytes (BERTOLINI)[12,13].

F. VERZÁR (Basel)

*Internal Tensions in the Collagen Macromolecule and their Changes with Ageing*

In the collagen macromolecule, for instance from tendon fibres, internal tensions are liberated by thermic or chemical action[14]. The measurement of these tensions by means of an *isometric method*[15], using fibres of constant diameter and length, produced the following results.

Tail tendons of rats of different ages were used. Their weight was about 5 mg for 10 cm of length. Their tension was measured at constant length in Ringer's solution. Temperature was raised from 55°C up to degrees of heat at which no further increase in tension, and the beginning of relaxation, showed that a maximal tension had been reached by heating. This point is expressed in g, as tension by 'thermic contraction'. The value increases with age, in confirmation of what has been described for the former ('isotonic') method, where the weight which inhibits thermic contraction was estimated[14].

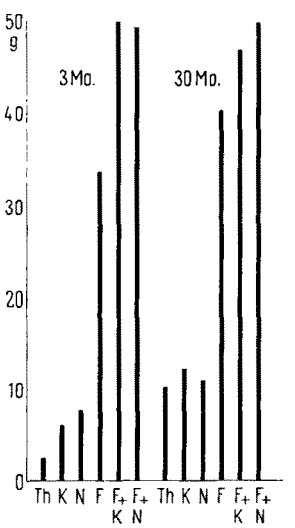
'Chemical contraction' was produced by means of potassium iodide, KI (40%) or sodium perchlorate, $NaClO_4$ (30%). At 30°C, contraction occurs in 10–20 min with KI and somewhat later with $NaClO_4$ to reach a maximal value. It is then followed by a relaxation.

The isometric measurement of tension is 30 to 50% greater by 'chemical' than by 'thermic' contraction (Table I). While with thermic contraction we have found a constant relation to age, this is not so clear in the case of chemical contraction. However, it is known, from the work of several authors who use chemical contraction as a test[16], that the values of 'relaxation' are related to age.

Tab. I

| No. | Age (months) | Tension in g Th. K. | $NaClO_4$ (30%) | KJ (40%) |
|---|---|---|---|---|
| 26 | 3 | 2.5 | 7.8 | 6.3 |
| 24 | 5 | 4.1 | 11.0 | 8.5 |
| 22 | 6 | 5.5 | 7.3 | 6.0 |
| 21 | 18 | 7.4 | 9.3 | 8.9 |
| 23 | 32 | 10.2 | 11.0 | 12.5 |
| 25 | 40 | 9.3 | 14.8 | 16.0 |

It is well known that *formaldehyde* has a tanning effect upon collagen[17]. Hydrogen or other bonds are produced[18,19]. After 10 min in a 1% solution of formaldehyde, the fibres become changed so that thermic contraction only begins at higher temperatures than formerly, and finishes at about 99°C, when relaxation sets in. The tension of young and old fibres mainly reaches equal values with formaldehyde. These tension values (e.g. about 38 g) are about ten times higher than the normal values for young, and four times higher than for old fibres at thermic contraction (Figure).




The Figure shows examples of tension measurements in g. A comparison is given of thermic contraction (Th), KI (K), $NaClO_4$ (N), formaldehyde 1% at 99° C (F), formaldehyde with KI (F + K), and formaldehyde with $NaClO_4$ (F + N) as described above.

[11] A. I. LANSING, *General Biology of Senescence*, in J. E. BIRREN (Ed.) *Handbook of Ageing and the Individual* (Chicago Univ. Press, 1959), p. 119.

[12] A. BERTOLINI, Gerontologia *6*, in print (1962).

[13] This work was done with a grant of the Muscular Dystrophy Association of America. We thank Prof. H. WILLENEGGER for a continuous supply of skin specimens. This work continues our former work with him[10].

[14] F. VERZÁR, Helv. physiol. Acta *13*, C64 (1955); *14*, 207 (1956).

[15] J. BROCA and F. VERZÁR, Gerontologia *5*, 223 (1961).

[16] M. CHVAPIL and Z. HRUZA, Gerontologia *3*, 241 (1959).

[17] I. BANGA, Gerontologia *1*, 325 (1957).

[18] F. VERZÁR and K. HUBER, Gerontologia *2*, 81 (1958).

[19] K. H. GUSTAVSON, *The Chemistry and Reactivity of Collagen* (Acad. Press, New York, 1956).

If these *formaldehyde-treated fibres* are then treated with substances which cause *chemical contraction* in normal fibres, such as KI or $NaClO_4$, then no tension develops at 30°C as it would in normal fibres. If, however, the fibres are heated to as much as 99°C (as with formaldehyde alone) the degree of tension which developes is larger than with formaldehyde alone. It was about 20 times the value for young fibres and 5 to 6 times that of old normal fibres (Table II).

Tab. II

| No. | Age (months) | Tension in g Th. K. | 1% HCOH | Same +40% KJ | Same +30% $NaClO_4$ |
|---|---|---|---|---|---|
| 26 | 3 | 2.5 | 34.0 | 50.0 | 49.4 |
| 24 | 5 | 4.1 | 38.5 | 67.0+ | 67.0+ |
| 20 | 6 | 6.3 | 45.0 | 56.3 | 63.6 |
| 21 | 18 | 7.0 | — | 67.2 | 67.2 |
| 19 | 32 | 10.2 | 40.5 | 46.8 | 50.0 |
| 25 | 40 | 9.3 | 37.2 | 57.8 | 59.7 |

The observation that maximal tension with KI and $NaClO_4$ is greater than with thermic contraction shows that these substances break more—or other—bonds than heat appears to do.

'Thermic contraction' is supposed to be the result of the breaking of the H-bonds, whereas 'chemical contraction' may break bonds of another type also.

Since the tension developed by formaldehyde tanning appears to be equal in young and old tendons, it follows that the loci of the bonds are not different in young and old collagen.

The fact that after formaldehyde treatment substances causing chemical contraction increase the tension after heating, shows that they liberate loci where more formaldehyde bonds can be produced. This again proves that chemical contraction influences other bonds than does thermic contraction[20].

F. Verzár (Basel

*Energy Metabolism and Phenomena of Senescence*

The analysis of the metabolic regulations which accompany senescence represents an essential line of research into its etiology. In this field we have studied the energy metabolism of the eye-lens and the artery wall, both well known for their relatively early ageing. In both tissues, nutrition occurs by imhibition, and both degrade from 70 to 80% of the glucose consumed through anaerobic glycolysis, and only 20 to 30% through respiration. These facts have been demonstrated by studying the metabolism of the lens, and the intima and media of the aortae or the arteries, in several species of vertebrates. So the tissues showing earlier senescence produce, for the same quantity of glucose consumed, approximately a third of the number of energy-rich bonds, as in ATP, compared with other organs such as the lungs, liver and brain. This poor energy yield, as seen *in vitro*, has been confirmed *in vivo* by the study of the distribution of free nucleotides, and particularly of energy-rich nucleoside triphosphates. It appears that the tissues with precocious senescence, and particularly the artery wall, are poor in highly phosphorylated nucleotides. With ageing, the amount of nucleoside polyphosphates, and consequently the available energy, is reduced; this is also seen in the study of the distribution of the free nucleotides. The cause of this reduction can be sought in the damage to the enzyme system, following various sorts of stresses which are practically inevitable in the life of the animal. In the organs poor in enzymes, as is the case in the eye-lens and the artery wall, a decrease in enzymatic activity will be noticed much faster than in tissues provided with better enzymatic equipment. The reduction of enzymatic activity, particularly that concerning the degradation of glucides, causes a diminution of the production of ATP. ATP is necessary for the synthesis of other nucleotides and nucleoside triphosphates such as GTP, UTP and CTP, with which it takes part in the synthesis of RNA. ATP also activates amino acids which, with the action of RNA and specific enzymes, assure the synthesis of the proteins and consequently of the enzymes as well. Finally ATP acts in the active transport of sugars and amino acids across the cell wall; this shows its importance in the nutrition of tissues. We have demonstrated the decrease of ATP with age, and verified that the mechanisms in which it participates (mentioned above) are also partially destroyed in the course of ageing. In this way, a decrease in the amount of RNA and the renewal of RNA and proteins has become evident. This last phenomenon, which shows signs of a difficulty in protein synthesis, is confirmed in the analysis of enzymatic activity. In fact the reduction of those activities as seen in the lens of the eye, and the arteries, can be considered to be a test for the slowing down of protein biosynthesis.

All this information together allows one to envisage the appearance, with age, of a vicious circle, and consequently a progressive reduction of the available tissue energy, and a slowing down of the renewal of tissue proteins which is an essential characteristic of life. In fact, the lowering of ATP synthesis brings about reductions in the syntheses of RNA, proteins, and some of the enzyme proteins. In turn, this last phenomenon brings about a sharp diminution of the oxidative phosphorylations and ATP production, which has new repercussions on the biosynthesis of enzyme proteins. This explains the fact that organs poor in enzymes, and having a metabolism with a low energy yield, represent a frail structure which enters the vicious circle faster, and grows old more quickly. An indication of the occurrence of this vicious circle is seen in the observation of an acceleration of the phenomena of senescence on the level of zones of aged cells of the eye lenses of old animals.

The report will appear in extenso in 'Revue Française d'Etudes Cliniques et Biologiques' and in 'Journal of Gerontology'.

P. Mandel (Strasbourg)

## Theme 3. Action of some External Factors on the Rate of Ageing.

*Introductory Comments to Theme 3*

Many causes for ageing have been discussed but it is very difficult to obtain direct experimental evidence bearing on its mechanism by studying senescent animals. One possible approach is to see the effect on life span of treatments which are known to produce specific lesions at the cellular level. Exposure to ionizing radiations is the best established method of reducing the average life expectancy of almost all forms of animal life. Unfortunately, radiations produce a very wide diversity of biological changes so that it is not possible to identify a particular mechanism which is responsible for the shortening of life span. Indeed it seems highly likely that different mechanisms apply under different conditions. Thus, in some mice whole body irradiation raises the leukaemia incidence to nearly 100% and the increase in death rate can then be attributed to the leukaemogenic action of radiation. With other strains malignancies are rare and yet radiation shortens life span. It seems unlikely that the radiation changes responsible for reducing the life span of insects are the same as those in mammals, since 100 times the dose is needed to produce effects in insects that are comparable to those in mammals.

The problem is not to determine a single mechanism for ageing, but to establish the contribution of different mechanisms in each situation. In different animals the relative importance of the different factors will vary widely. An important first step is to establish the influence of different and well defined changes ranging from somatic mutations to the impairment of the function of specific organs.

Improved understanding of the mode of action of drugs seems to place a powerful tool into the hands of the gerontologist.

P. Alexander

[20] This work was done with the support of the Muscular Dystrophy Association of America.

*The Effect of some Chemical Mutagens on the Life Span of Mice*

The reduction in the expectation of life which follows the exposure of mammals to ionizing radiations has been attributed to the induction of mutations in somatic cells. If this process contributed significantly to the shortening of life span, mutagenic chemicals would be expected to bring about a similar effect. A nitrogen mustard and a related bifunctional alkylating agent—myleran—did shorten the life span of mice, but these agents bring about many biological changes. In addition to the induction of mutations, they are truly radiomimetic in the diversity of their biological effects.

The monofunctional alkylating agent, ethyl methane sulphonate (EMS)—$CH_3CH_2OSO_2CH_3$—is an exceptionally powerful mutagen, but unlike radiation and nitrogen mustards is not cytotoxic to dividing cells.

The administration of high doses of EMS had no effect on life span, although the effect of such treatments on spermatogenesis strongly indicates that the animal cells were, in fact, subjected to mutagen action. EMS induced kidney and lung tumours in our CBA mice, but these appeared so late in the life of the animal that the life expectancy was not thereby significantly decreased. While not conclusive, these experiments suggest that the induction of somatic mutations is not the principal factor responsible for the shortening of life span by radiation, or indeed for normal senescens. Possible other mechanisms were discussed.

P. ALEXANDER and Miss D. I. CONNELL (London)

*Biologic Age Measurements in Hiroshima Atomic Bomb Survivors*

The Atomic Bomb Casualty Commission in Hiroshima and Nagasaki (Japan), has been conducting broad health surveys, aimed primarily at disease detection, in bomb survivors and control subjects in the two cities since 1947. The epidemiological plan of these studies has varied, but since 1958 a fixed population sample of irradiated and non-irradiated subjects have been undergoing sequential medical examinations at 2 year intervals. These examinations are expected to continue for an indeterminate period.

Because of the widely held hypothesis that irradiation induces a non-specific acceleration of ageing processes, it was decided to study methods of assessing 'biological' as contrasted to chronological age. The plan was, first, to study individual physiological variants for their general suitability in a clinical epidemiological study; second to study the statistical interrelationships of the individual test; and, finally, to establish an ageing test battery that would be used in sequential examinations to establish a biological age.

The first objective, study of a number of individual tests, has been accomplished. Our second objective, analysis of statistical interrelationships, has been completed in a preliminary fashion but requires further refinement. It is hoped that an operational ageing test battery will be instituted in 1962.

The present report deals largely with the results of the individual tests performed in 500–1500 subjects undergoing examination. With single tests, at one point in time only, no differences between irradiated and non-irradiated subjects were expected and none was found. The tests studied included: hair graying, skin elasticity, ocular accommodation, hearing acuity, electrocardiographic changes with age with calculation of an 'EKG ageing score', a complex test of reaction time, hand grip, peripheral nerve sensitivity as measured by a vibrometer, serum isagglutinin titer, and erythrocyte agglutinability. The results of these tests will be shown, and their suitability in an epidemiological study of human ageing discussed.

J. W. HOLLINGSWORTH (Yale)

*Experimental Investigations on the Action of Sulphapyrimidine in Geriatric Individuals*

In feeding tests on mice, rats and dogs it was noticed that animals fed with sulphapyrimidine compounds especially with Sulphadiazine (= Debenal = Adiazine) were in better general condition and lived longer than the controls.

In further tests one tried to see whether this effect was also noticeable in animals with pronounced signs of old age. Endogenous hereditary factors have a hand in promoting the appearance of geriatric symptoms. There are rat inbred strains where the animals clearly show senile symptoms when they grow very old, while in other strains there are no such signs of ageing. Signs of senility and geriatric diseases such as loss of hair, senile cataract, old-age cachexia, and old-age arthritis are frequently seen in dogs and these diseases appear differently in different breeds. It is suggested that it is hardly likely that one can actually influence physiological consequences of the process of ageing by means of drugs. A rejuvenation cannot be expected. However, apart from the inevitable ageing process, many old individuals suffer from certain diseases which are often seen in old age but which do not affect all aged people.

It is difficult to draw a line between the physiological ageing processes in the different systems of the organism, as ectodermal tissues, the endocrinous organs, circulatory organs, and between characteristic, frequent diseases in old individuals. There is no reason why these diseases should not respond to suitable treatment.

Experimentally we can produce significant improvement in behaviour and in geriatric diseases in old animals (mice, rats and dogs) by feeding sulphapyrimidine in small doses. Photographs and a film show the influence of treatment in senile rats and dogs. The mechanism of action is not yet known. Other workers found that feeding chicks with sulphonamide derivatives of pyrimidine led to hypertrophy of the testicles and observed that Debenal, contrary to other sulphonamide derivatives, inhibited the lipase activity. The most interesting indication in geriatric humans is the beginning of senile cataract, in which are observed a certain percentage of cases with improvement of eyesight. This observation was confirmed in France by VOISIN and PAQUELIN.

CHR. HACKMANN (Wuppertal-Elberfeld)

*Effects of Sulfonamides on Ageing of Rats*

Based on the experiments of HACKMANN (Münch. med. Wschr. *100*, 1814, 1958) who described a 'revitalising effect' of chronical low administration of a sulfonamide (Debenal), we started systematic feeding of sulfonamides to inbred white female rats of different ages in 1959.

Four different groups were formed: in the first, 28 animals aged 503 ± 24 days and 12 aged 953 ± 32 days were given Debenal (sulfonamide D). In the second group, 36 animals aged 673 ± 14 days and 7 aged 912 ± 63 days were given a sulfonamide with prolonged action (sulfonamide B). In the third group, 10 animals aged 503 ± 0 days and 20 aged 839 ± 38 days were given a sulfonamide without bacteriostatic action (sulfonamide A). 55 animals aged 500 days served as controls.

According to HACKMANN, the dosage of the substances was 30 g sulfonamide to 15 kg of food, or 0.2%.

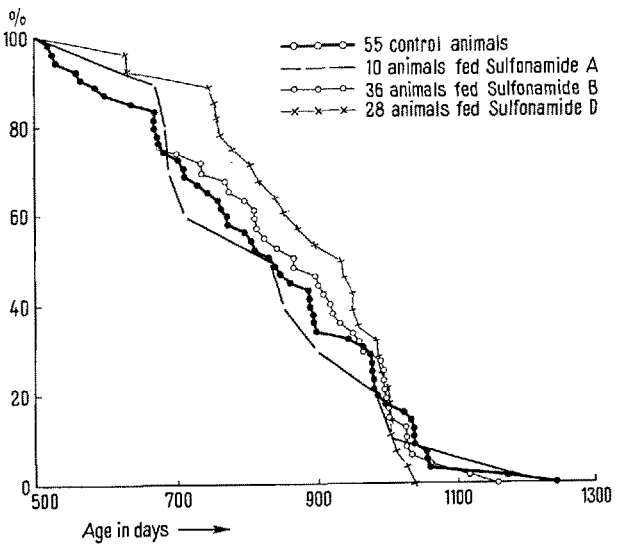



Fig. 1. Survival curves of animals fed sulfonamides from the age of 500 to 600 days on.

Calculation of *average life-span* (Table 1) gave no difference between the control groups and the animals fed sulfonamide A or B, either when fed to younger or older animals. A slight increase in average life-span was observed for animals fed Debenal.

Figure 1 shows the *survival curves* for animals fed the different sulfonamides from the age of 500 to 600 days on. It can be seen that 54% of the animals fed Debenal reached the age of 900 days compared with 34% of the controls. 18% of both groups reached the age of 1000 days. At 1037 days all animals fed Debenal had died, whereas 9% of the controls were still alive, the oldest control animal reaching the age of 1244 days. An apparently favorable effect on survival is thus seen only in the first 200 to 400 days of feeding, after which mortality is parallel to the control curve. After 500 days of feeding, mortality in the Debenal-fed animals is greater than in the controls.

Figure 2 shows the survival curves for animals fed sulfonamides from the age of 840 to 950 days on. It can be seen that if Debenal was fed to very old animals (953 ± 32 days) 5 out of 12 animals survived 1100 days compared with 2 out of 18 control animals. The oldest sulfonamide-fed animal died at 1342 days, compared with 1244 days for the oldest control animal. On the average these animals received Debenal for 154 ± 109 days. This apparently favourable effect of Debenal when fed for a relatively short time to very old animals needs careful interpretation. Such animals represent a selection with incontrollable variances.

*Inspection* of the animals showed that animals fed Debenal in general had smoother and whiter hair than the controls. Animals fed sulfonamide A or B in general looked more yellowish and more

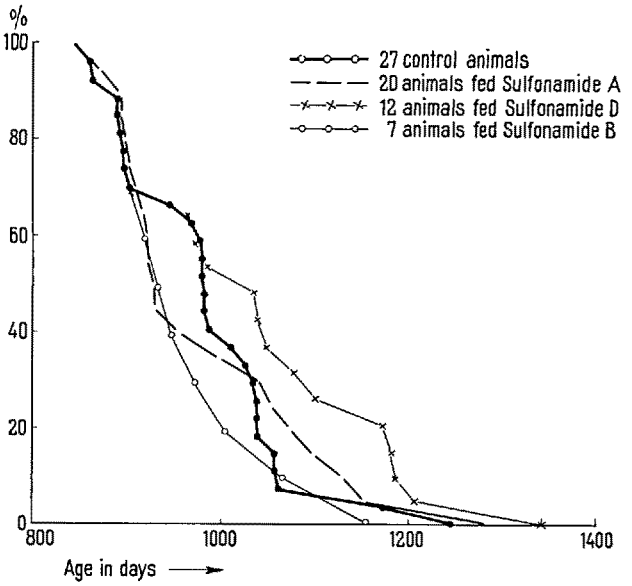



Fig. 2. Survival curves of animals fed sulfonamides from the age of 840 to 950 days on.

Tab. I. Average life-span

| Sulfonamide | Sulfonamide fed animals: Number of animals | Age at beginning of feeding (days) | Average life-span | Control animals[a]: Number of animals[a] | Age at beginning of experiment (days) | Average life-span | |
|---|---|---|---|---|---|---|---|
| Sulfonamide D | 28 | 503 ± 24 | 888 ± 120 | 55 | 500 ± 0 | 834 ± 172 | n.s. |
| | 12 | 953 ± 32 | 1107 ± 111 | 17 | 960 ± 0 | 1033 ± 72 | $0.05 > p > 0.01$ |
| Sulfonamide B | 36 | 673 ± 14 | 916 ± 113 | 42 | 675 ± 0 | 904 ± 134 | n.s. |
| | 7 | 912 ± 63 | 1000 ± 82 | 19 | 900 ± 0 | 1028 ± 75 | n.s. |
| Sulfonamide A | 10 | 520 ± 0 | 853 ± 222 | 55 | 500 ± 0 | 834 ± 172 | n.s. |
| | 20 | 839 ± 38 | 985 ± 113 | 27 | 840 ± 0 | 984 ± 92 | n.s. |

Tab. II. Average weight at different ages
(three and six months after feeding of sulfonamides)

| | Sulfonamide D | | Sulfonamide B | | Sulfonamide A | |
|---|---|---|---|---|---|---|
| | Test animals | Controls | Test animals | Controls | Test animals | Controls |
| Number of animals | 26 | 22 | 27 | 23 | 10 | 22 |
| Age/days | 486 ± 0 | 500 ± 0 | 657 ± 15 | 643 ± 29 | 520 ± 0 | 500 ± 0 |
| Average weight/g | 300.1 ± 28.7 | 289.6 ± 25.7 | 308.9 ± 31.9 | 293.6 ± 34.2 | 310.6 ± 43.4 | 289.6 ± 25.7 |
| Age/days | 578 ± 0 | 586 ± 0 | 760 ± 13 | 742 ± 25 | 611 ± 0 | 586 ± 0 |
| Average weight/g | 309.4 ± 30.5 | 300.2 ± 31.9 | 280.1 ± 28.9 | 287.6 ± 35.9 | 282.4 ± 29.8 | 300.2 ± 31.9 |
| Age/days | 670 ± 0 | 682 ± 0 | 822 ± 13 | 834 ± 37 | 650 ± 0 | 682 ± 0 |
| Average weight/g | 305.3 ± 33.6 | 294.9 ± 21.5 | 275.6 ± 28.7 | 281.6 ± 44.2 | 270.3 ± 43.8 | 294.9 ± 21.5 |
| Difference in weight after three months | +9.3 ± 17.9 | +10.6 ± 17.8 | −28.8 ± 12.9 | − 6.0 ± 16.9 | −28.2 ± 15.4 | +10.6 ± 17.8 |
| Difference in weight after six months | +5.2 ± 23.0 | + 5.3 ± 23.7 | −33.3 ± 25.8 | −12.0 ± 31.6 | −40.3 ± 15.1 | + 5.3 ± 23.7 |

dishevelled than the controls. The amount of animals classified as having specially good hair during their whole life was 41% among the controls and 57% among animals fed Debenal, against 13% with sulfonamide A and 31% with sulfonamide B.

*Weight controls* (Table II) showed no difference between body-weights of Debenal-fed animals and controls, whereas animals being given sulfonamide A or B lost between 20 to 40 g on the average in the first six months of feeding.

*Pathological symptoms* (paralysed legs, general atrophy, diarrhoea, genital bleeding, urinary incontinency, etc.) were more frequent in the sulfonamide-fed groups than in the controls, but less frequent in the Debenal group than in the two other sulfonamide groups.

*Post mortem inspections* showed no difference in the frequency of infections of the lung in the different groups. Tumours of the genital organs were found in 26% in group A, 25% in group B, 24% in group D. No tumours of the genital organs were found among the controls. In group A and D animals which had been given sulfonamides since the age of 500 days showed tumours in 43 and 40% against 18 and 25% in the groups which had been given sulfonamides only after the age of 790 days. Tumours in the subcutis of the abdomen were found in 20% in group A, 19% in group B, 29% in group D and 18% in the controls.

These observations with Debenal and a not bacteriostatic other sulfonamide (A) do not support the hypothesis that better survival during the first 200 to 400 days of feeding is caused by bacteriostatic effects.

D. GSELL (Basel)

## 4. Miscellaneous Communications

*Age Variations of the Calcium Urinary Excretion in Clinically Normal Subjects*

The variations with age of the daily renal excretion of calcium has been studied in 201 normal individuals (99 males and 101 females), 25 to 75 years old, together with bone density, urea clearance, serum cholesterol and $\beta$-lipoproteins. The daily calcium excretion was found to decline regularly with age among men, whereas the average values increased slightly in women up to the age of 45 to decline later on. Serum cholesterol and $\beta$-lipoproteins are consistently higher in subjects having the highest values of urinary calcium.

This paper has been published in the 'Revue Française d'Études Cliniques et Biologiques' 7, 535 (1962).

F. BOURLIÈRE and J. DRY (Paris)

*Age, Population Density and Catecholamine Excretion in Rats*

The urinary excretion of catecholamines has been studied in ten adult rats, aged 8 to 20 months, during two consecutive months. No differences have been found between the average values of urinary catecholamines among the younger and older animals. No difference has been found, moreover, between rats kept under various degrees of crowding.

R. HERBEUVAL, G. MASSE, and M. L. CHOLLOT (Nancy)

*General Conclusions of the Examination of People Aged One Hundred Years in Hungary*

According to the data of the census taken in 1960, the number of the inhabitants of Hungary was 9,976,500. Out of these, 34 were aged one hundred years or more, documented with official papers. Out of the 34, 23 were investigated in detail, because 11 died before the beginning of the medical examinations. The 23 inhabitants, aged one hundred years or more, were controlled by a research group consisting of a gerontologist, statistician, anthropologist, internist, surgeon, ophthalmologist, dentist, radiologist and nutritionist.

General conclusions are given of the medical control of these 23 people aged one hundred years or more.

L. HARANGHY and E. BEREGI (Budapest)

*The Effect of Restricted Feeding on Growth and Longevity on Fish*

COMFORT reported upon current studies of life length in populations of *Lebistes* grown at different rates and checked by reduced feeding for different periods. Up to 1,500 days, the present status of the experiment, slowly grown or checked fish had shown a very significantly higher survival than rapidly grown brood-mates kept in opposite ends of the same tank and in the same environment. This work will be reported when the survival curves are complete.

A. COMFORT (London)

## IN MEMORIAM

## Paul Hoffmann

*1. Juli 1884–9. März 1962*

Mitten aus unermüdlichem Schaffen heraus starb unerwartet am 9. März 1962 PAUL ALBIN HOFFMANN, emeritierter Ordinarius der Physiologie an der Universitat Freiburg im Breisgau. Noch hatte er sich mit Freuden zur Teilnahme am XXII. Internationalen Physiologenkongress in Leiden angemeldet; und er hätte es als eine Selbstverständlichkeit betrachtet, mit über 78 Jahren eine eigene experimentelle Arbeit vorzutragen. Dies war ihm leider nicht mehr vergönnt, und so werden Physiologen aus allen Teilen der Welt wenige Monate nach seinem Hinschied seiner überragenden Persönlichkeit und seiner wissenschaftlichen Leistungen gedenken.

PAUL HOFFMANN wurde am 1. Juli 1884 in Dorpat in Lettland geboren, wo sein Vater Professor für innere Medizin war. Der junge HOFFMANN studierte Medizin in Leipzig, Marburg und Berlin, legte 1908 in Leipzig sein medizinisches Staatsexamen ab und promovierte ein Jahr später zum Doktor der Medizin mit einem «Beitrag zur Kenntnis der sogenannten Kittlinien der Herzmuskelfasern». Assistent war er vorerst am Physiologischen Institut in Berlin unter RUBNER, wo PIPERS elektrophysiologische Untersuchungen an menschlichen Muskeln für die wissenschaftliche Laufbahn des angehenden Physiologen bestimmend sein mussten. Von Berlin kam HOFFMANN zu M. VON FREY nach Würzburg. Dort habilitierte er sich 1912 mit einer Arbeit über «Die Aktionsströme des mit Veratrin vergifteten Muskels». 1917 wurde er zum ausserordentlichen Professor ernannt und 1924 als ordentlicher Professor und Nachfolger von J. VON KRIES auf den Lehrstuhl für Physiologie an die Universität Freiburg im Breisgau berufen. Während dreissig Jahren bekleidete er dieses Amt, in welchem ihm neben Genugtuung und Erfolgen als Forscher und Lehrer auch schwere Schicksalsschläge nicht erspart blieben. Nicht nur verlor er durch den zweiten Weltkrieg drei seiner besten Schüler, sondern es wurde im Herbst 1944 auch noch sein Institut durch Bombardierung zerstört. Ungebrochen arbeitete er weiter, plante das neue Institut, in das er noch einziehen und als Emeritus bis zum Tag vor seinem Tode weiter experimentieren konnte.

PAUL HOFFMANNS wissenschaftliche Leistungen liegen auf dem Gebiet der Innervation der Skelettmuskulatur; und zwar sind es ganz besonders die Reflexphysiologie und damit die Bedeutung des Nervensystems für die Motorik, die durch seine experimentellen und auch angewandt-physiologischen Arbeiten in einzigartiger Weise gefördert wurden. Frei und unabhängig von konformistischer Einstellung ging er seine eigenen als richtig erkannten Wege, schuf er wesentlich neue Begriffe und wurde er zum führenden Forscher und Lehrer der Neurophysiologie, dem als Zeitgenossen auf dem europäi-