external pressure by direct fluid transmission) the vessels lining the cavity will respond in the same way.

The best-known situation in which this occurs is the middle-ear cavity when descending in an aircraft. While at altitude the pressure in the middle ear falls, as air can always escape passively from the eustachian tube. As the aircraft descends the barometric pressure rises, and unfortunately air will not passively re-enter the eustachian tube but must be made to do so by a conscious effort. If this effort is not made or is inefficiently carried out, or if the eustachian tube is blocked by an infection of the upper respiratory tract, the pressure in the middle ear falls below that in the rest of the body. The vessels in the middle ear are then passively dilated, with consequent reddening of the drum and transudate into the middle-ear cavity, so-called aero-otitis media (Armstrong, 1939). The indrawing of the drum which occurs is a mechanical concomitant of these effects and not their cause. Its main danger is that rupture occurs when the mechanical tolerance of the drum is exceeded, but pain and deafness occur before this limit has been reached and, most significantly, remain long after the drum has returned to its normal position.

The same mechanism explains the haemoptysis which sometimes occurs in those who dive without breathing apparatus. When diving with the breath held the thoracic cage must collapse to equalize the pressure in the lungs; this process is limited when the lungs approach residual volume. If the diver descends below this point the pulmonary vessels dilate and may rupture. This injury occurs in native pearl-divers and skin-divers using schnorkel masks. Infection of the upper respiratory tract may close the ostia of the paranasal sinuses, converting them into closed spaces in which a falling pressure can cause similar bleeding in addition to pain and congestion.

The danger of reversed ear is created by anything which closes off the external auditory canal, and ear-plugs are worse in this respect than a frogman's suit. They should never be worn when diving or when travelling by air; when descending in either situation they may not only cause reversed-ear injury but may be driven inwards by the increasing pressure and cause direct trauma of the drum. If an amateur skin-diver wishes to wear a suit in cold waters he should choose one made of porous rubber. This will never cause reversed ear, as a porous material cannot possibly maintain a partial vacuum, and the petechiae which form in the skin under the wrinkles of a watertight suit are, of course, never seen. A porous type of suit maintains body temperature quite efficiently, as it fills with and holds water in the same way as a woollen garment normally fills with and holds air.

Barotrauma may occur in other artificial cavities; some goggles worn by amateur skin-divers form a closed cavity in front of the eyes, and diving in these has caused serious conjunctival haemorrhage. Goggles worn for this purpose should cover the nose as well as the eyes so that air can be blown into them to equalize pressures during descent.

Summary

The clinical features, treatment, and prevention of the reversed-ear syndrome are discussed. It is a condition of barotrauma to the external auditory canal and is characterized by petechiae, bullae, and rupture of the skin in the meatus. It occurs when the pressure in the

external canal falls 100–200 mm. Hg below that in the body tissues, in which circumstance the blood-vessels in the skin will be passively dilated to give rise to these signs. The syndrome has been produced and observed experimentally since its original observation among professional divers. Similar injury will occur in any body cavity which falls below external pressure, and the significance of this in aviation and diving is discussed.

I am grateful to Petty Officer H. Eccleston, who acted as subject in some of these experiments; to Petty Officer G. Brown for his assistance and musical accompaniment; and to the Medical Director-General of the Royal Navy for permission to publish these findings.

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PLASMA CHOLESTEROL LEVELS IN NEW ZEALAND

OBSERVATIONS IN 1,000 URBAN MALES

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In New Zealand the high incidence of deaths due to coronary artery disease is similar to that found in other highly westernized countries such as the United States of America, Australia, Canada, and the United Kingdom (World Health Organization 1955, 1956). Numerous well-planned surveys throughout the world have shown the close association between the prevalence of coronary artery disease in a population on the one hand and the mean blood cholesterol concentrations on the other (Keys *et al.*, 1952, 1958; Bronte-Stewart *et al.*, 1955). Relatively high cholesterol levels have been found in inhabitants of some of the aforementioned countries—for example, the United States and the United Kingdom—and also in Finland. In populations so characterized, one of the most constant features has been the trend for cholesterol levels to increase with age (Keys *et al.*, 1950, 1958; Keys, 1956; Lawry *et al.*, 1957; Lewis *et al.*, 1957).

From New Zealand—a country reputed to have a *per capita* consumption of total fat as high as or higher than in any other nation (Food and Agriculture Organization, 1955)—there have been no previous surveys relating to blood cholesterol values in the population.

The study to be described was undertaken in 1,000 apparently healthy adult males from an urban community. The purpose was to determine the mean fasting plasma cholesterol levels and to analyse such findings in relation to occupation, body weight, and smoking habits at various ages. While, as might be expected, the major findings are similar to those noted in other westernized communities, there are certain features which differ and give food for further thought.

Materials and Methods

The 1,000 male subjects, aged from under 20 to over 60 years, were all symptom-free, apparently healthy, and actively employed. They came from two large broad occupational groups, 500 being manual workers in one industrial concern (manufacturing railway locomotives and equipment), the other 500 from sedentary and semi-sedentary occupations of varying nature—professions, business executives, accountants, clerks, shopkeepers, taxi-drivers, school teachers, students, etc. — all volunteers.

Besides age and occupation, a record was made of height to the nearest half-inch and of weight (stripped) to the nearest pound, and smoking habits were standardized to the number of cigarettes per week. Oxalated blood samples were taken at 8 a.m. with the subjects in the fasting state for at least 10 hours. Total plasma cholesterol concentrations were estimated in duplicate—individually by both of us—using the method of Zlatkis *et al.* (1953) as modified by MacIntyre and Ralston (1954), and a mean of the duplicate was taken as the final value. Between groups of 50 duplicate observations there was a standard error of 6.53 mg.

Results

Mean Plasma Cholesterol Levels and Age

The mean levels according to five-year age-groups are shown in Table I. There is a wide but consistent

TABLE I.—*Plasma Cholesterol Levels in 1,000 Apparently Healthy New Zealand Males (Urban Community)*

Age-group	No.	Mean Cholesterol Level (mg./100 ml.)	S.D.	Coefficient of Variation
15-19 years	75	187	33.3	18%
20-24 "	138	207	37.9	18%
25-29 "	87	221	39.1	18%
30-34 "	112	231	39.4	17%
35-39 "	117	242	40.3	17%
40-44 "	110	247	37.3	15%
45-49 "	160	248	39.6	16%
50-54 "	128	243	38.9	16%
55-59 "	52	240	37.5	16%
60-64 "	14	236	39.5	17%
65-69 "	7	215	35.5	17%
Total	1,000	231	42.6	18%

standard deviation for each group. The mean level for 1,000 males for all ages is 231 mg./100 ml. However, from a mean level of 187 mg./100 ml. in age-group 15-19 there is a progressive increase in levels with age to a maximum mean of 248 mg. in age-group 45-49. Thereafter, as illustrated in the fitted-trend curve (Fig. 1), from a turning point calculated to be around 47 years of age there is a subsequent slight decline in values.

FIG. 1

FIG. 2

FIG. 3

FIG. 1.—Plasma cholesterol change with age in 1,000 New Zealand males. FIG. 2.—Mean plasma cholesterol levels in two main occupational groups. (Fitted-trend curves.) FIG. 3.—Mean plasma cholesterol levels according to relative weights. (Fitted-trend curves.)

Occupation

According to age, the mean levels in 500 industrial manual workers are compared with the levels observed in the composite 500 sedentary and semi-sedentary group ("white-collar" workers) (Table II and Fig. 2).

TABLE II.—*Comparison of Mean Plasma Cholesterols in the Two Main Occupational Groups*

Age-group	Industrial Workers		White-collar Group		Student's "t"
	No.	Mean Cholesterol Level (mg./100/ml.)	No.	Mean Cholesterol Level (mg./100/ml.)	
15-19 years	48	180	27	200	$t=2.63$; d.f.=73 $0.01 < P < 0.02^{**}$
20-24 "	70	201	68	212	$t=2.90$; d.f.=223 $0.001 < P < 0.01^{**}$
25-29 "	39	211	48	230	
30-34 "	52	222	60	239	$t=2.85$; d.f.=227 $0.001 < P < 0.01^{**}$
35-39 "	59	236	58	249	
40-44 "	47	244	63	250	$t=1.79$; d.f.=268 $0.05 < P < 0.10$
45-49 "	80	242	80	253	
50-54 "	66	238	62	248	$t=1.48$; d.f.=178 $0.10 < P < 0.20$
55-59 "	28	238	24	242	
60-64 "	7	224	7	247	$t=0.03$; d.f.=19 $0.90 < P$
65-69 "	4	236	3	187	
Total	500	224	500	238	$t=5.24$; d.f.=998 $P < 0.001^{***}$

The overall mean cholesterol levels for the two general occupational groups are 224 mg./100 ml. for the industrial workers and 238 mg./100 ml. for the white-collar workers. The decade levels in the white-collar group exceed those in the industrial group throughout. The differences in values, particularly noticeable in the younger age-groups, are highly significant both in the total sample and in the decades below 40 years of age (see P values in Table II).

Relative Weight

At the time of the study the degree of obesity of subjects could not be measured more directly. Relative weights, estimated to obtain a crude sample of overweight individuals at one end of the scale, were evaluated by taking the actual weight of each subject expressed as a percentage of the so-called standard weight for a man at that age and height. Standard weights were obtained from the tables for weight and age of the Metropolitan Life Insurance Company of the U.S.A. Although these figures are based on American standards we have taken them as a useful dividing line to classify our subjects into low, medium, and high relative weights; in particular to separate off the high-relative-weight group, who, as others have indicated, consist largely of the clinically obese subjects. In this series this group constituted approximately 10% of the total sample and were distributed approximately

equally in the two occupational groups. Thus *high*-relative-weight (overweight) subjects had weights over 120% of the standard weight, *medium* were between 120% and standard, and *low* were under the standard weight.

In view of the method used to assess overweight it was thought justifiable only to compare the cholesterol levels of the high-relative-weight group with the low- and medium-relative-weight groups combined. Comparison by five-year age-groups showed that in the groups below 40 years of age the mean levels in the overweight subjects exceeded those in the remainder but not to a statistically significant degree. At ages of 40 years and above there were no such differences.

If the total sample is examined—omitting 31 subjects in whom data were incomplete, those aged 60 and over because of insufficient numbers and those under 20 because they were regarded as actively growing—then in the 20–59 year age sample of 873 subjects the mean cholesterol level of 84 overweight subjects (243 mg./100 ml.) exceeds that in the rest (234 mg./100 ml.), but again not to a highly significant degree. However, as shown in Table III, if a division of this

TABLE III.—Relative Weights and Mean Cholesterol Levels

Relative Weight Group	No.	Mean Cholesterol Level (mg./100 ml.)	
A. All Age Groups 20-59 Years			
High	84	243	} 234
Medium	437	234	
Low	352	233	
B. Older Age-groups 40-59 Years			
High	40	244	} 244
Medium	210	246	
Low	185	242	
C. Younger Age-groups 20-39 Years			
High	44	241	} 223
Medium	227	223	
Low	167	222	

t = 1.88; d.f. = 871
0.05 < P < 0.10

t = 0.08; d.f. = 433
0.9 < P

t = 2.75; d.f. = 436
0.001 < P < 0.01

whole 20–59-year age sample is made equally by age into an older sample of 40 and above and a younger sample below 40 years, then comparison of the mean cholesterol levels between the overweight group and the combined low- and medium-relative-weight groups reveals highly significant findings dependent upon age. Whereas in the older (40–59-year sample) there is no difference in levels between the overweight and the rest—244 mg./100 ml. in both groups—in the younger (20–39-year sample) the overweight subjects have a mean cholesterol level of 241 mg./100 ml. compared with 223 mg./100 ml. in the rest, a difference which is highly significant in that the probability that this has occurred by chance is less than 1 in 100 but greater than 1 in 1,000.

Smoking Habits

To assess the degree of smoking, the subjects were classified according to their habits as follows: Group A, non-smokers. Group B, smokers of from 1 to 99 cigarettes a week. Group C, smokers of from 100 to 199 cigarettes a week. Group D, smokers of 200 or more cigarettes a week. As there was an obvious deficiency of heavier smokers in the younger age-group and a proportionate excess in the older age-group, it was not possible to evaluate the effect of smoking in all age-groups together or singly—as has been done with other factors. We have therefore taken for analysis the most important age-group—that is, from 40–59 years. As within this group there is no trend of

changing smoking habits with age, nor is there any overall association between overweight and tobacco smoking, it is valid to compare the various smoking categories and in the comparison any difference is not due to age or overweight. As shown in Table IV, if

TABLE IV.—Plasma Cholesterol Levels and Smoking Habits in 450 Males Aged 40–59 Years

Group	No.	Mean Cholesterol Levels (mg./100 ml.)			
A	159	248	248	245	245
B	118	240	} 244	} 247	} 246
C	148	247			
D	25	246			

A: Non-smokers
B: 1–99
C: 100–199
D: 200+ } cigarettes/week

non-smokers are compared with smokers of all categories combined, a cholesterol mean of 248 mg./100 ml. is seen in non-smokers in contrast to a mean of 244 mg./100 ml. in the smokers—a difference which is of no significance whatsoever. Comparing non-smokers with group D or group D and C smokers combined, or comparing non-smokers and group B smokers with smokers of group C and D combined, however contrasted, no differences in mean cholesterol values can be discerned. Separate analyses for both industrial and white-collar groups showed identical findings.

Discussion

Age-Trend in Cholesterol Levels

The pattern of age-trend in cholesterol levels described in this study conforms closely to that generally noted by many but not all observers in other highly westernized communities, particularly in the United States (Keys *et al.*, 1950; Lawry *et al.*, 1957; Lewis *et al.*, 1957). However, slight and possibly suggestive differences are noted.

(1) The maximum mean values obtained in this study are slightly higher than in the surveys of Lewis *et al.* (1957) and Lawry *et al.* (1957) in the United States, but they are less than the mean values reported from Finland by Keys *et al.* (1958). In view of the variability of methods of cholesterol determination between laboratories, considerable caution must be exercised in drawing any conclusions from these apparent international differences, which therefore are noted merely for what they are worth.

(2) Perhaps more significant in our survey is that with the age-trend the turning-point in our decreasing values is around 47 years, compared with around 55 years as noted by Lewis *et al.* (1957). Some have postulated that this late age-trend in mean cholesterol levels observed in surveys of this nature may be—at least partially—the consequence of excessive deaths among subjects with higher cholesterol levels, hence diminishing the mean normal levels in the later age-groups (Lawry *et al.*, 1957). On this hypothesis one might suggest further the possibility that the turning-point in our males coming some eight years before that reported in the several American series may be reflecting a “coronary loss” operating at an earlier age in New Zealand males; but this is mere speculation.

Occupation and Cholesterol Levels

The finding of distinct and significant differences in mean cholesterol levels between the two broad occupational groups is particularly interesting in view of the relationship claimed to exist between occupational

status and both coronary mortality rates and the degree of ischaemic myocardial fibrosis found at necropsy (Morris *et al.*, 1953; Morris and Crawford, 1958). As indicated in Fig. 2, the two fitted-trend curves of cholesterol levels with age show an approximation in the later decades, the turning-point for the white-collar group being earlier than that for the industrial group—that is, around 45 years, as opposed to around 48 years of age. Again, on speculation such findings might suggest disproportionate “coronary loss” from the white-collar as opposed to the industrial middle-aged group. Whether these cholesterol patterns are related to possible differences in social status, physical activity, or diet, etc., between the two groups cannot be commented on at this stage.

Overweight and Cholesterol Levels

Most published reports have indicated that serum cholesterol levels are not greatly influenced by the presence of overweight. However, there is a certain amount of evidence that an individual's serum cholesterol increases while he is actually putting on weight (Mann *et al.*, 1956; Gordon *et al.*, 1958). Although in the present study there has been no true measure of obesity, the division of subjects by relative weight has given a crude sample of overweight individuals who could be accepted as clinically obese. The positive correlation between cholesterol levels and overweight in the younger subjects in contrast with the older subjects was unexpected. The significance of this finding is a matter of conjecture. Possibly the increase in cholesterol levels in the overweights of the younger decades is related to a period of rapid weight increase. On the other hand, a positive correlation might have extended into the later decades but for the fact that a relatively greater number of overweight subjects may have developed coronary disease, leaving a residual apparently healthy sample with lower mean cholesterol levels. It is interesting that on these fitted-trend curves of cholesterol levels with age the turning-point towards decreasing levels is around 41 years in the overweight subjects compared with 47 years in the remainder. That obese subjects do succumb to coronary disease more readily seems to be very probable (Gubner, 1957; Dawber *et al.*, 1957).

Smoking Habits and Cholesterol Levels

Smoking and coronary disease have been linked together for many years, more recently since a positive relationship was indicated between them in several major statistical surveys (Doll and Hill, 1956; Hammond and Horn, 1958; Buechley *et al.*, 1958). In general it has been maintained that the coronary mortality rates for men who smoke 20 cigarettes or more daily generally exceed the corresponding rates for non-smokers.

Investigating serum cholesterol levels in relation to smoking habits, others, such as Miller *et al.* (1958) in the U.S.A. and Karvonen *et al.* (1959) in Finland, have reported significantly higher levels in smokers than in non-smokers. Our own observations are therefore in contrast to these surveys, but are consistent with the findings of Gofman *et al.* (1955), who found that although heavy smokers in the 20–39-year age-group had higher cholesterol values than non-smokers this was not so in the 40–59-year age-group. Because of the deficiency of heavy smokers in our 20–39-year age-group it has not been possible to examine for any

similar age-trend in our subjects. Perhaps there is a trend dependent on age comparable to that which we have noted in respect to occupational status and overweight.

Summary

Fasting plasma cholesterol levels have been estimated in 1,000 apparently healthy New Zealand urban males, and a statistical analysis of the mean levels has been undertaken in relation to age, occupation, relative weight, and smoking habits.

The trend of mean levels rising with age to a maximum mean of 248 mg./100 ml. between 45 and 49 years of age, then of a subsequent decline, conforms to the general pattern reported by others in westernized communities, except that the turning-point towards decreasing levels occurs at an earlier age.

Mean levels in “white-collar” workers exceeded those in age-matched industrial workers under 40 years of age with highly significant differences, but there was an approximation of levels in the later decades.

Excessively overweight subjects (10% of the total as assessed by relative weights) had mean levels significantly higher than in the remaining subjects in the 20–39 years sample, this being in contrast to the finding in the 40–59 years sample, in which both the overweight and the remaining subjects had identical mean levels. No difference in mean cholesterol levels was found between non-smokers and smokers of any grade in the 40–59-year age-group.

The different age-trends in cholesterol values in relationship to general occupational status and to the presence or otherwise of overweight is discussed speculatively in respect of possible differences in coronary mortality rates in middle age. The importance of the age factor in assessing these relationships, particularly between overweight and cholesterol levels, is stressed.

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CARCINOMA AND CUSHING'S SYNDROME

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[WITH SPECIAL PLATE]

Though it is common at necropsy to find adrenal metastases from primary bronchial carcinoma, these do not usually give rise to any clinically recognizable endocrine disturbance. On the other hand, patients with bronchial carcinoma may very occasionally manifest the biochemical or even full clinical features of Cushing's syndrome. This subject has recently been fully reviewed by Allott and Skelton (1960), and mention has been made of primary sites of carcinoma other than the bronchus. It is worth drawing attention to this association between carcinoma and adrenocortical overactivity, partly to avoid the erroneous diagnosis that the primary neoplasm lies in the adrenal cortex, and partly to prevent the patient undergoing a fruitless adrenalectomy when a primary neoplasm elsewhere is unsuspected. Bagshawe (1960a) has pointed out that the finding of marked hypokalaemic alkalosis in a patient with adrenocortical overactivity should arouse strong suspicion of a primary neoplasm, most commonly in the bronchus.

Two further cases of this association are reported here. In each it was considered at one time that the primary carcinoma might be present in the adrenal.

Case 1

The patient, a housewife aged 57 years, was admitted to Harefield Hospital on October 23, 1959, chiefly because of mental disturbance. Over the preceding three months there had been a gradual and progressive change of mood with alternating bouts of depression and elation, sometimes with aggressive outbursts, sometimes with grandiose delusions of wealth and largesse. The first physical symptom noticed by the patient was swelling of the legs and arms in May, 1959, followed later by swelling of the face. Treatment by diuretics led to some improvement in the arms, but her legs became progressively larger, as did her face. Her weight greatly increased and she became much more breathless on exertion. She noticed a dry mouth, but did not mention undue thirst or polyuria. There was no complaint of

muscular weakness. She smoked 20 to 30 cigarettes daily, and had suffered from a cough for 20 years. No relevant past or family history was obtained.

On admission she was garrulous and sometimes confused. There was marked generalized pigmentation of the skin, largely racial in origin, but considered by her husband to have increased from its previous level. The buccal mucous membrane was not pigmented. Extensive purpura was present over both forearms, and purple striae were noted in the skin of the abdomen and buttocks. There were typical fatty deposits over the trunk, face, and neck. Hirsuties was not marked. Pitting oedema of the lower limbs was not associated with raised jugular venous pressure. The blood-pressure was 150-190/90-110 mm. Hg. Hess's capillary fragility test was negative. Crepitations were heard over the left lower lobe of the lung. Both ankle-jerks were absent, but no sensory abnormalities were detected. The urine contained 2% of sugar and a trace of acetone.

Investigations

Investigations showed marked hypokalaemia (serum sodium 150, potassium 2.3, chloride 99 mEq/l.). The salivary potassium concentration was 23 and sodium 5.6 mEq/l., giving a Na/K ratio of 0.24. The blood sugar was 316 mg. per 100 ml. 1½ hours after a meal, and a glucose-tolerance test showed a fasting level of 166 mg. per 100 ml., rising in 1½ hours to 253 mg. and falling in 2½ hours to 205 mg. per 100 ml.; all specimens of urine contained sugar. Urinary 17-ketosteroid excretion was 60.2 mg. and 17-ketogenic steroids 30.8 mg. in 24 hours. Other findings were as follows: Hb 11.2 g. per 100 ml.; M.C.V. 98 cμ; M.C.H.C. 32%; white cells 7,000 per c.mm. (85% neutrophils); platelets 120,000 per c.mm.; normal bleeding and clotting times; E.S.R. 60 mm. in first hour (Westergren); blood urea 45 mg. per 100 ml. Chest radiographs initially showed only cardiac enlargement, but subsequently patchy consolidation of the left lower lobe appeared. Prednisone did not significantly reduce the daily output of 17-ketosteroids, and this feature, together with the finding of a raised β-fraction, was considered to suggest an adrenal carcinoma as the cause of her clinically diagnosed Cushing's syndrome.

Progress

Potassium chloride by mouth in increasing doses up to 10 g. daily resulted in only a slight rise in the low serum level, though never to normal, the highest being 3.5 mEq/l. Glycosuria was controlled by soluble insulin, the daily requirement ranging between 20 and 60 units. Penicillin was given for the apparent infection in the left lower lobe of the lung, which was associated with a low-grade fever, and the signs improved, though not completely. Three weeks after admission there was an episode of right-sided colic associated with the passage of blood-clots in the urine. A hard, fixed mass was felt deep in the right loin, and a hard mass arising out of the pelvis. Hirsuties became more marked, extensive fresh purpura developed, the platelet count decreased progressively to 35,800 per c.mm. four weeks after admission, and the haemoglobin fell to 8.5 g. per 100 ml. Blood transfusion was refused.

She was transferred to Hillingdon Hospital on November 22, a month after her original admission, for further investigations with a view to adrenalectomy. Coarse crepitations were still present over the left lower lobe, where the percussion note was moderately impaired and breath sounds were diminished. Investigations confirmed the persistent hypokalaemia (3.5 mEq/l.), not associated, however, with alkalosis (serum bicarbonate 25 mEq/l.). For the first time some myelocytes were seen in the peripheral blood. The urine grew a *Proteus* on culture. Shortly after transfer her temperature and pulse rate rose rapidly and her general condition deteriorated. A blood-stream infection was suspected and subsequently confirmed, a *Proteus* being grown. Tetracycline, penicillin and streptomycin, and erythromycin were variously given without avail and she died on November 28, 1959.