Summary

An attempt has been made to sift some of the clinical experience from 155 consecutive cases of persistent ductus arteriosus. The results of surgery in 138 of these cases are presented briefly, together with the management of the 17 not submitted to operation. Experience is discussed and present policies are outlined in dealing with this abnormality in children and adults and when it is complicated by pulmonary hypertension and bacterial endarteritis.

We thank our colleagues in the cardio-surgical unit for permission to present this work. The operations were performed by Mr. Douglas Robb and one of us (R.N.). The help of Miss Catherine Tibbles, of the Central Medical Library, of Dr. Stephen Williams, pathologist, and of Mr. Burge, of the clinical photographic department, is acknowledged.

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VARIATION OF PLASMA ELECTROLYTE AND TOTAL PROTEIN LEVELS IN THE INDIVIDUAL

BY

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For a proper interpretation of biochemical results in disease one requires a knowledge of the variation found in the healthy population, such variation establishing a "normal range." The variations found in a healthy individual from day to day (the temporal variation) and within each day (diurnal variation) are also important. In the present study the concentrations of plasma sodium (Na), potassium (K), chloride (Cl), total carbon dioxide (T.CO₂), and total protein (Pr) are reported in a healthy group and in healthy individuals over a period of time. Since basal conditions cannot always be assured when taking blood for analysis, the possible effects upon these biochemical values of posture, meals, moderate exertion, and the menstrual cycle were investigated.

Experimental Procedures

Subjects.—Group A: Single samples of venous blood were taken from 25 healthy men and 25 healthy women between the ages of 20 and 35 years. Group B: Blood

was taken on 10 occasions over periods of two to six months from each of four healthy young men and four healthy young women. Group C: Blood was taken from each of five young men at approximately equal intervals throughout a single day. Three were healthy ambulatory subjects and two were convalescent patients lying in bed. Normal diets of known composition were eaten, and intake and output balances for the electrolytes and water throughout the day were calculated. Group D: Blood was taken twice a week from two young women during two consecutive menstrual cycles and from a third during one menstrual cycle.

Methods.—Venous blood was taken without stasis into a heparinized syringe and centrifuged under paraffin without delay. 0.04 ml. of heparin (5,000 units per ml.) was used for 10 ml. of blood. Most specimens, except under Group C, were taken between 10 a.m. and noon, and not less than one hour after meals or vigorous exertion. In studying the women in groups A and B, samples were taken so that all stages of the menstrual cycle were equally represented. Analytical methods were as follows: Na and K, using a laboratory-made flame photometer employing coal-gas and compressed air, a light filter system, and an external standard; Cl, Sanderson's (1952) potentiometric method; T.CO₂ content, Van Slyke and Neill's (1924) manometric method; Pr, a semi-micro Kjeldahl procedure (Fawcett, 1954). Analyses were performed at least in duplicate. The coefficient of variation (due to analytical error) was found to be as follows: Na, 0.5%; K, 1.0%; Cl, 0.6%; T.CO₂, 0.8%; Pr, 1.0%; and for duplicate analyses the figures would be: Na, 0.4%; K, 0.7%; Cl, 0.4%; T.CO₂, 0.6%; Pr, 0.7%.

Results

The electrolyte and protein results are expressed in terms of mean values ($\bar{m}$) and standard deviations (σ). This is valid because the results from the healthy subjects in group A are each distributed in the form of a Gaussian (normal) curve. Wootton and King (1953) observed a similar distribution except in the case of K, in which it was lognormal. Josephson and Dahlberg (1952), however, found a Gaussian distribution of K in health. The plasma electrolyte and protein results in groups B, C, and D are also distributed in Gaussian curves about the individual's mean level.

Table I reports the mean values, standard deviations, and 95% ranges of Na, K, Cl, T.CO₂, and Pr for 25 healthy young men and 25 healthy young women. The standard

TABLE I.—Plasma Electrolyte Concentrations (mEq/l.) and Total Protein Concentrations (g./100 ml.) in 25 Healthy Young Men and 25 Healthy Young Women

	Na	K	Cl	T.CO ₂	Pr
Mean ($\bar{m}$) for men	141.7	4.11	101.8	29.5	7.33
Standard deviation (σ) for men	1.0	0.27	1.4	1.6	0.25
95% range for men ($\bar{m} \pm 2\sigma$)	139.7–143.7	3.57–4.65	99.0–104.6	26.3–32.7	6.83–7.83
Mean ($\bar{m}$) for women	140.5	4.12	103.0	28.1	7.30
Standard deviation (σ) for women	1.7	0.32	1.2	1.6	0.32
95% range for women ($\bar{m} \pm 2\sigma$)	137.1–143.9	3.48–4.76	100.6–105.4	24.9–31.3	6.66–7.94
Value of t for sex difference	3.1	0.12	3.2	3.2	0.29
Probability level for sex difference	0.001 < P < 0.01	0.1 < P	0.001 < P < 0.01	0.001 < P < 0.01	0.1 < P

deviations and ranges are less than those generally reported—for example, Wootton, King, and Maclean Smith (1951), Josephson and Dahlberg (1952), and Wootton and King (1953). This may be attributed to our narrower age group and to the different chemical methods employed. The following differences between the sexes, all highly significant statistically, were detected. In women Na is 1.2 mEq/l. lower, Cl is 1.2 mEq/l. higher, and T.CO₂ is 1.4 mEq/l. lower than in men. There is no difference of K or Pr between the sexes. The standard deviation for Na is greater in women than in men.

Table II shows the mean values and standard deviations of the plasma electrolytes and total protein for each of four healthy young men and four healthy young women from whom blood was taken on 10 occasions during periods of two to six months. The standard deviations for Cl, T.CO₂, and Pr in these individuals are about three-quarters of those for the population (Table I), suggesting that their temporal variation is less than the variation in the population as a whole.

The standard deviations for Na and K are greater in some individuals than in the healthy population (Table I); this can be accounted for as follows. The results in Table I were all obtained within one month, whereas those in Table II were obtained over a period of six months, during which period there was a mean fall of about 1% in the levels of Na and K which may have been due either to seasonal variation or to systematic analytical errors. If either of these explanations is correct, the individual's temporal variation over a period of a few weeks must be even less than indicated by our figures for Na and K. There is no evidence that the temporal variation, as measured by the standard deviation, of any of these electrolytes is markedly greater in either men or women.

Table III presents the findings of an analysis of variance comparing the variation between individuals with the variation within each individual, and is based on the results

TABLE II.—*Plasma Electrolyte Concentrations (mEq/l.) and Total Protein Concentrations (g./100 ml.) in 10 Samples from Each of Eight Healthy Subjects over Periods of 2 to 6 Months*

Subject	Na	K	Cl	T.CO ₂	Pr
Men:					
K. K. { m σ ..	142.7 2.6	3.90 0.24	99.9 0.8	31.6 1.4	7.38 0.15
G. H. { m σ ..	141.6 1.7	4.15 0.24	100.6 1.0	31.1 1.2	7.11 0.13
J. F. { m σ ..	142.7 1.7	3.50 0.33	101.5 1.0	29.9 1.2	7.19 0.18
V. W. { m σ ..	141.5 0.8	4.01 0.40	101.8 1.0	29.0 1.4	7.60 0.17
Women:					
P. B. { m σ ..	141.9 1.6	4.06 0.15	104.0 0.7	28.5 1.4	—
E. L. { m σ ..	140.5 1.0	3.88 0.19	102.5 0.8	28.3 1.2	—
E. W. { m σ ..	140.5 1.7	4.20 0.22	102.6 1.2	27.2 1.2	—
M. M. { m σ ..	141.3 1.3	4.17 0.40	105.0 1.3	26.2 1.4	—

TABLE III.—*Analysis of Variance: Between Individuals: Within Individuals*

		Na	K	Cl	T.CO ₂	Pr
Men ..	Variance ratio	1.3	8.1	7.9	8.4	11.4
	Probability level ..	0.2 < P	P < 0.001	P < 0.001	P < 0.001	P < 0.001
Women	Variance ratio	2.3	3.1	12.9	6.6	—
	Probability level ..	0.05 < P < 0.2	0.01 < P < 0.05	P < 0.001	0.001 < P < 0.01	—

reported in Table II. The evidence is significant that the variation within individuals is less than that between individuals in the case of K, Cl, T.CO₂, and Pr but not in the case of Na. Excluding Na, therefore, it seems that each individual tends to maintain his own characteristic electrolyte and total protein pattern.

Table IV reports the mean values and standard deviations of the plasma electrolytes and total protein for each of five young men from whom several samples of blood were taken during the course of one day. Three of these men (J. F., V. W., and B. H.) were healthy subjects carrying out their usual duties, involving only slight physical exertion; the other two (F. O. and T. I.) were convalescent patients lying in bed. J. F. and V. W. had been studied over several months, as reported in Table II. The standard deviations

TABLE IV.—*Plasma Electrolyte Concentrations (mEq/l.) and Total Protein Concentrations (g./100 ml.) in Five Young Men During the Course of One Day*

Subject	No. Samples	Na	K	Cl	T.CO ₂	Pr*
J. F.	6 { m σ	142.5 0.4	3.36 0.13	104.2 1.2	28.1 1.3	7.00 0.13
V. W.	10 { m σ	139.9 0.8	3.95 0.11	101.7 1.6	26.7 1.1	7.66 0.19
B. H.	7 { m σ	142.2 0.7	3.46 0.14	100.4 0.9	30.4 1.5	7.32 0.14
F. O.	10 { m σ	139.8 0.7	4.00 0.19	99.1 1.0	30.7 1.1	7.38 0.20
T. I.	10 { m σ	139.9 0.9	4.18 0.21	101.8 0.8	28.4 0.6	6.97 0.19

* In the ambulatory subjects the "before-rising" specimens were excluded from the calculation of m and σ because change of posture affects Pr. The "before-rising" levels were: J. F., 6.5; V. W., 7.3; B. H., 6.4.

of Cl, T.CO₂, and Pr are similar to those in Table II, suggesting that the variation of Cl, T.CO₂, and Pr is as great within one day as from one week to another. The standard deviations of Na and K are somewhat less than those in Table II.

The standard deviations of T.CO₂ and Cl are only slightly greater in the ambulatory subjects than in those in bed, and the standard deviations of Na, K, and Pr are no greater. Light exertion thus has little effect on the constituents studied. We found, however, that the effect of 30 minutes' vigorous exercise was to depress T.CO₂ by 3–9 mEq/l. and to elevate Cl by 1–4 mEq/l. Na, K, and Pr were unaffected.

Fig. 1 shows the variation of electrolyte and protein levels from each subject's mean level for the day. For this purpose the results upon which Table IV is based are grouped into two-hourly periods. There appears to be no regular diurnal change of the electrolyte pattern. We were unable to observe any consistent change in electrolyte levels on rising from bed corresponding to the large changes of plasma protein concentration reported by Perera and Berliner (1943) and confirmed in the present investigation. Pr rose by 0.5 g./100 ml. in J. F., by 0.4 g./100 ml. in V. W., and by 0.9 g./100 ml. in B. H. on rising from bed. About half an hour after a meal Cl usually fell by about 2 mEq/l., and T.CO₂ rose by a corresponding amount, but we noted several exceptions to this. Food intake resulted in no consistent change in Na, K, and Pr.

FIG. 1.—Deviation from the individual's mean plasma electrolyte and protein values in each of five young men during one day. In ambulatory subjects, "before-rising" levels are marked with crosses. These were excluded from the calculation of mean protein values. M.=mean.

Fig. 2 shows the actual electrolyte and protein levels found in two typical diurnal studies, one on an ambulatory subject (V. W.) and one on a patient in bed (F. O.).

Fig. 3 reports our results on plasma electrolyte and protein changes in relation to the menstrual cycle. Blood was taken twice a week from two healthy young women during two consecutive menstrual cycles and from a third during one menstrual cycle. The mean value of all results for each four-day period measured from the start of menstruation is plotted with its 95% confidence limits. The mean value of Na for the period 8-4 days before the start of menstruation is 2.2 mEq/l. lower than for the period 12-16 days afterwards. The difference is highly significant ($0.001 < P < 0.01$).

FIG. 2.—Variation, in one day, of plasma electrolyte and protein levels of one ambulatory subject (V. W.) and one subject confined to bed (F. O.). Continuous line, subject V. W.; dotted line, subject F. O. R, rose from bed; B, breakfast; L, lunch; D, dinner.

FIG. 3.—Variation of plasma electrolyte and protein levels in relation to the menstrual cycle: mean values and 95% confidence limits. The values corresponding to 16-12 days before the start of menstruation are not identical to those for 12-16 days afterwards because these subjects had 25-, 27-, and 32-day cycles respectively.

The mean value of T.CO₂ for the period 4-0 days before menstruation is 2.85 mEq/l. lower than for the period 8-12 days after ($0.001 < P < 0.01$). The variations of Na and T.CO₂ roughly parallel each other. The mean value of Cl for the period 4-0 days before the start of menstruation is 1.7 mEq/l. higher than for the period 8-12 days after ($0.01 < P < 0.02$). Cl usually varies in the opposite direction to T.CO₂. K is highest during the first four days of menstruation, but this is not statistically significant. There is no evidence that plasma total protein concentration varies significantly in relation to the menstrual cycle.

Discussion and Conclusions

Josephson and Dahlberg (1952) made a detailed study of biochemical variations due to age, sex, and season. The blood constituents studied by them, relevant to the present work, were serum sodium, potassium, protein, and blood chloride. They detected no sex difference in Na or Pr, a doubtful sex difference in K, and a higher blood chloride in women than in men. Unfortunately the long-term nature of their survey necessitated using chemical methods current in 1946, and there appears to be no equally comprehensive published work in which more modern and reproducible methods were employed. Hald, Heinsen, and Peters (1947) observed statistically significant sex differences in plasma chloride and bicarbonate concentration, the former being 2.6 mEq/l. higher and the latter being 2.5 mEq/l. lower in women than in men. In our study similar but smaller differences were observed. We also found that Na was significantly higher in men than in women.

It is clear from our results that the ranges of plasma Na, K, Cl, T.CO₂, and Pr concentration in a group of healthy young men and women are small, and perhaps less than is generally appreciated. In the individual under fairly stable conditions the levels of these plasma constituents remain remarkably constant within the day and over a period of months.

In the healthy individual, plasma electrolyte (Na may be an exception) and total protein concentrations vary less over a period of months than the variation found within a group of healthy people. This has been demonstrated previously in the case of total protein, albumin, and globulin (Fawcett and Wynn, 1956). Thus plasma electrolyte and protein levels generally regarded as "normal" may be outside the usual ranges of some individuals.

We were unable to demonstrate any regular diurnal influence upon plasma electrolytes or protein except for the elevation of protein concentration on rising from bed. Violent exertion can have a gross effect on T.CO₂ and Cl, but otherwise we have no reason to suppose that basal conditions must be observed when blood is taken for electrolyte analysis. Indeed, such changes as occurred during our diurnal experiments were often unassociated with any ascertainable cause. For example, in B. H. the Na rose by 1.5 mEq/l. in 15 minutes, during the whole of which time he was carrying out a simple laboratory procedure.

The menstrual cycle has an influence on plasma electrolyte but not on protein concentrations. The effect is too small to be of clinical importance.

As plasma electrolyte and protein levels in health show only small variations, we conclude that the methods used for their analysis in clinical biochemistry must be highly reproducible if the smallest alterations due to disease are to be detected.

Summary

The ranges of plasma sodium, potassium, chloride, total CO₂, and total protein levels in 25 healthy young men and 25 healthy young women are remarkably small.

There are differences due to sex which are statistically significant in the cases of Na, Cl, and total CO₂.

The temporal variation of plasma K, Cl, total CO₂, and total protein levels in eight healthy young subjects

is significantly less than the variation between them. Therefore these levels tend to be characteristic of the individual, and values generally regarded as "normal" may be outside the usual ranges of some individuals.

There is no definite diurnal variation of plasma electrolyte or protein levels. The influence of rising from recumbency, normal meals, moderate exertion, and the menstrual cycle is discussed.

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INTRACRANIAL ANEURYSM

A NEW METHOD OF SURGICAL TREATMENT

BY

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The purpose of this preliminary communication is to record the successful treatment of aneurysms of a type hitherto considered manageable only by the uncertain method of muscle-wrapping. Certain aneurysms, notably those with a broad neck, though suitable for ligation, are associated with a spasm of local arteries after operation which can disastrously affect the result of treatment.

Technique

The method provides an unyielding investment for the sac and parent vessels, and rupture of the sac is rendered impossible almost at once. So far the self-curing acrylic, methyl-methacrylate, has been found most suitable. The substance is applied in a semifluid state, before polymerization is complete.

Application is simple, using a dental syringe and an empty cartridge—a wide-bore cannula delivering the medium, which flows over the sac and invests vessels where they enter and leave it.

The polymer can be autoclaved, after which it requires pounding in a mortar, and is put up in empty dental anaesthetic cartridges. (Sterilization in a dry oven results in a fusion of the polymer.) The monomer, sterilized by passage through a Seitz bacterial filter, is introduced into the polymer by needle puncture of the cap of the cartridge. Proportions are a matter of experience—roughly three of powder to one of liquid. Vigorous shaking promotes an even mix. When it is of the consistence of thick cream, it is ready for use. Polymerization is complete in 15 to 20 minutes, and by that time the material has set quite firm. Heat production during polymerization is only slight; 115° F. (46.1° C.) was the highest temperature recorded.

An acrylic compound was selected because it is known to

withstand continuous immersion in salinous fluids, its surface sets smoothly, there is no shrinkage during polymerization, and there is neither clinical nor experimental evidence yet of any adverse local reaction to its presence. Arterial spasm is not produced, either immediate or delayed.

Preliminary experiments on animals revealed no contraindications to its trial in operations for aneurysm. Dr. R. M. Norman, of the Burden Mental Research Institute in Bristol, and Dr. R. J. Sandry, of Frenchay Hospital Pathological Department, reported on the appearance of tissues removed up to intervals of two months after application of material to the brain surface, within the subarachnoid space, and around major vessels of limbs. In their opinion, a surprisingly slight reaction to the presence of acrylic substance was revealed, consisting merely of slight increase of microglia in the molecular layer of cortex. The neurones were not damaged, nor were there any detectable adverse effects on the wall of limb vessels.

For comparison, bone wax introduced into the subdural space produced microscopical evidence of greater damage to the cerebral tissue.

Results

Recently four cases presented which could not have been treated by clip or ligature, and muscle-wrapping would have been unsatisfactory because of the distribution of entering and leaving vessels. The method here described was used. The lesions in three cases are reproduced diagrammatically. The chiasm was always screened from the acrylic by gutta-percha tissue, removed later.

Arteriograms obtained before the patient's discharge from hospital have shown that the aneurysms remain patent but smaller. Obviously, clotting within these aneurysms now becomes undesirable with this new method. Where direct ligation is indicated, there is an advantage in having a method less traumatic than clips for repair of the sac, but a large flat clip can be used if the sac ruptures, the clip being applied at any convenient distance from the neck (if possible) to secure haemostasis, and the distal part of the sac cut away. The clip, sac, and parent vessel can then be invested. A procedure such as this might be found desirable when the aneurysm is large. Premature rupture during dissection under hypothermia may be treated by temporary proximal clipping or ligation of the parent vessel and investment. This was practised in the fourth case, an aneurysm of the dominant middle cerebral, branches of which were coursing over and adherent to the sac, which had a broad neck.

Arterial spasm, which presents such a hazard clinically to these patients, may be prolonged by the presence of clips or ligature abutting on the parent vessel. The clinical and experimental evidence suggests that local arterial spasm does not occur when the acrylic material is applied.

An Explanation

It seems to be necessary to explain why the above information is presented with a follow-up interval which does not exceed six months. Because the method provides what, so far, appears to be a safe and simple method of preventing rupture of aneurysms, particularly those not suit-

A, Anterior communicating aneurysm; abnormal vascular pattern. B, Middle cerebral aneurysm. C, Anterior cerebral aneurysm.