THE SALT EXCRETION OF MILIARIA SUBJECTS*

L. J. A. LOEWENTHAL, M.D., M.R.C.P.,‡ W. M. POLITZER, M.D.,† AND C. H. WYNDHAM, M.B., B.CH., M.R.C.P.¶

The role of sodium chloride in the aetiology of miliaria rubra has formed the subject of previous publications.[1, 2] In these it was shown that cellular oedema of the sweat ducts constituted the earliest histological change in this disease, and that similar changes could be produced by sodium chloride applied as a compress or introduced by iontophoresis. It was also reported that many residents in the tropics, as well as older texts on tropical diseases, maintained that sea-bathing was a predisposing cause of miliaria. This impression was confirmed by the evidence of physicians obtained during a recent tour of Arabia and the Persian Gulf;[3] fresh water showers taken immediately after sea-bathing tended to prevent or minimize attacks of miliaria; and some stations that had a bad reputation for miliaria provided only sea-water for domestic bathing.

In deep-level gold miners in South Africa, among whom there is a high incidence of miliaria, there is no contact with *exogenous* hypertonic salt solutions, such as sea-water ; but *endogenous* salt is brought to the skin surface in the sweat, and it was suspected that this might be a factor in the causation of miliaria in this population.[1] The present experiment was therefore designed to test this hypothesis by comparing the excretion of sodium chloride in chronic miliaria subjects with that of controls. Chronic sufferers were selected purposely, for a first attack during acclimatization is seen in a majority of gold miners.

MATERIALS AND METHODS

Subjects

Three groups of adult White males were selected:

A. *10 miners, subjects of chronic miliaria.* Of these 5 had been deemed unfit for underground work and had been in surface employment for from 8 months to 3 years. During this time they had been free of clinical manifestations of miliaria. One of the remainder had recently suffered from a single attack lasting 2 months and contrasted with the remaining 4, who had frequently relapsed.

B. *6 miners who had never had miliaria,* or had experienced a single, transient attack on becoming acclimatized many years before.

C. *6 normal non-miners, who had never had miliaria,* nor been exposed to the necessary conditions of heat and humidity.

As far as possible, subjects of comparable age and physique were selected. Those of groups A and B had worked for a similar number of years in the same or similar mines, doing identical work. The areas in which miliaria had occurred usually recorded temperatures of 90 - 105°F. (dry bulb) and 80 - 95°F. (wet bulb), and rock-face temperatures of 120°F. or more were common. Other factors in their normal working conditions, such as ventilation and physical exertion, might vary considerably from day to day or hour to hour. Table I shows the principal data applicable to the subjects.

TABLE I. PHYSICAL DATA OF THE EXPERIMENTAL GROUPS

Group	*Particulars*	*No.*	*Mean age*	*Mean weight in lb.*	*Years of service underground*
A	Miliaria subjects	10	39	176	12·2
B	Control miners	6	34	175·5	14·7
C	Control non-miners	6	33	168·3	—

The dietary salt intake of these groups was unknown. All the miners (groups A and B) were married men and ate the food prepared by their wives; the majority in both groups denied adding extra salt at table and one may assume that their intake would depend on their wives' taste and would therefore be comparable in the two groups. Although salt tablets are provided in the mines, none of the subjects in either group were in the habit of taking these while at work.

Conditions of the Experiment

The men were exposed in groups of two in the climatic chamber to a moderate degree of heat and work stress. These comprised 5 hours of intermittent work and rest in an air temperature of 93°F. and a wet-bulb temperature of 90°F. Air movement was 100 ft./min. The surrounding surfaces were at air temperature. The men worked for half of every hour and rested for the remaining part of the hour. Work comprised stepping on and off a stool 1 foot in height at a rate of 6 times per minute. The average rate of oxygen consumption (i.e. rest plus work) for men of this weight is 0·5 litres/min.

At the end of each hour the interscapular area was washed with distilled water, and fresh sweat was then collected in a chemically clean test tube closed with a rubber stopper. Five such hourly collections were made. The total urine passed during and immediately after the experiment was likewise collected in a stoppered container.

The following data were recorded hourly during the experiment: heart rate, oral temperature, skin temperature, weight, water intake in ml., urine passed (if any) in ml., calculated sweat rate, and calculated state of dehydration from initial weight.

*Presented at the South African Medical Congress, Johannesburg, July 1963. The work was supported by a grant from The Rand Mutual Assurance Company Limited, Johannesburg.

†From the South African Institute for Medical Research, Johannesburg.

‡From the Chamber of Mines Hospital, Johannesburg.

¶Professor of Physiology, University of the Witwatersrand: Director, Applied Physiology Laboratory, The Chamber of Mines, Johannesburg.

TABLE II. MEANS AND STANDARD DEVIATIONS OF DATA OBTAINED

Group		Na in sweat (mEq./l.)					Cl in sweat (mEq./l.)					Na in urine (mEq./l.)	Cl in urine (mEq./l.)	Cl loss in urine (G)	Estimated Na loss in sweat (G)	Na loss in urine (G)	Mean total Na (G)	State of dehydration at 5 hours (G)
		1	2	3	4	5	1	2	3	4	5							
A		71·2	81·9	88·8	95·9	98·1	65·3	78·1	84·2	89·6	93·3	130	176·0	1·16	3·93	0·58	4·51	1904
	SD	27·51	27·44	23·22	24·58	30·44	22·92	23·49	20·73	26·17	23·07	19·16						
B		40·2	51·5	63·7	71·5	76·5	37·5	49·2	59·3	68·3	72·2	93·7	145·2	0·71	2·33	0·28	2·61	1754
	SD	10·86	16·67	21·35	27·86	28·58	11·66	16·82	20·83	28·25	29·34	34·27						
C		41·8	56·9	72·8	70·1	85·2	38·8	56·3	71·6	70·8	82·2	113·5	175·0	0·98	1·49	0·39	1·88	1009
	SD	18·81	26·08	22·25	33·27	26·66	16·00	23·17	21·49	28·14	27·20	26·21						

A = Miliaria (miners). B = Controls (miners). C = Controls (non-miners). SD = Standard deviation + —.

Laboratory methods. Sweat and urinary chloride determinations were carried out by means of the Cotlove automatic titration unit.[4, 5] Sweat and urinary sodium were estimated with an Eel flame photometer.[6] Tests were performed by duplicate estimation and results showed close agreement.

RESULTS

No appreciable differences between groups were noted as regards temperature or weight change.

Sodium and Chloride Concentrations in Sweat

The ratio of sodium to chloride approached unity in all sweat samples, the former invariably giving a slightly greater value; this incidentally provided a check on the accuracy of the laboratory techniques. Fig. 1 represents graphically the mean hourly concentrations of sodium for the 3 groups; Table II gives the mean values and standard deviations for the same; and comparisons between groups are shown in Table III, using Student's 't' test of significance for small samples.

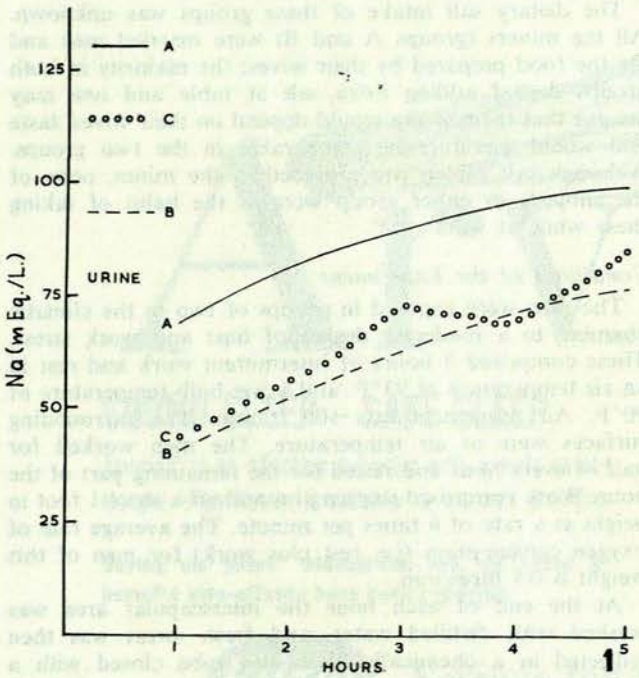

Fig. 1. Hourly sodium concentrations in the sweat of groups A, B and C. Sodium concentrations in total urine.

It will be observed that differences between group A on the one hand, and groups B and C on the other, are significant after 1 hour and that, when groups B and C are combined as a single control group, there is a highly significant difference after 1 hour and a difference of lower significance after 2, 3 and 4 hours. A striking fact was that only one subject of group A showed values below the means of those in the control groups. This was the subject previously mentioned, who had recently suffered from a single episode of 2 months' miliaria. *Conversely, no member of the control groups showed a 1-hour salt concentration as high as the mean of group A.*

An estimate of the total amount of sodium lost in the sweat was made by calculating the volume of sweat produced from the weight loss, water intake and urine output; the mean sodium concentration in the sweat over 5 hours, converted from mEq./l. into G. per litre, then allowed an estimate to be made. The results so obtained show that the miliaria subjects not only produced a higher concentration of sodium in their sweat, but also lost a significantly larger quantity.

TABLE III. LEVEL OF SIGNIFICANCE (P) IN COMPARISON OF 3 GROUPS

Groups compared		A : B	A : C	B : C	A : B+C
Na (sweat)	1 hour	·05	·05	NS	·01
	2 hours	·05	0·1	NS	·05
	3 hours	·05	NS	NS	·05
	4 hours	NS	0·1	NS	·05
	5 hours	NS	NS	NS	NS
Cl (sweat)	1 hour	·05	·05	NS	·01
	2 hours	·05	0·1	NS	·05
	3 hours	·05	NS	NS	·05
	4 hours	NS	NS	NS	0·1
	5 hours	NS	NS	NS	NS
Estimated Na loss in sweat		NS	·01	NS	·02
Na concentration in urine		·05	NS	NS	·05
Na loss in urine		·05	NS	NS	0·1
5-hour state of dehydration		NS	0·1	NS	NS
Heart rate		—	—	—	·01

Note: The above results are obtained by the 't' test. Levels of ·05 to ·01 are regarded as 'significant' to 'highly significant'. NS and 0·1 are 'not significant'.

Urine

The miliaria group showed a significantly higher figure for sodium concentration than group B, or groups B and

TABLE IV. MEANS OF HEART RATES, ORAL TEMPERATURE AND SWEAT RATES

Group	Heart Rates Hours						Oral Temperature Hours						Sweat Rates Hours					
	0	1	2	3	4	5	0	1	2	3	4	5	0	1	2	3	4	5
A	89	126	131	134	141	143	98·7	100·1	100·0	100·1	100·1	100·1	1	440	550	507	427	343
B	80	106	113	116	121	113	98·3	99·7	99·6	100·0	99·9	99·9	1	353	519	504	507	375
C	76	110	109	118	121	126	98·5	99·3	99·6	99·6	99·7	99·7	1	232	415	338	353	293

C combined (Fig. 1). The average total loss of sodium in the urine of group A is also significantly greater than that in group B; this finding, to be discussed later, is of great importance. The urinary chlorides show far less difference between groups.

State of Dehydration

The hourly sweat rates (Table IV) of the miliaria subjects were greater than those of the controls, although not significantly so (at the 95% level). All groups drank water *ad libitum* and at the end of the 5th hour the miliaria men were dehydrated to the extent of 1,904 G., compared to 1,754 and 1,009 G. of the control groups (Table II); the differences were not significant at the 95% level.

Heat Regulation

The initial weights of the groups were similar. The mean rate of heat production of the groups would therefore be similar also. Sweat rates, replacement of fluid losses, and temperatures (Table IV) showed no significant differences. The two significant differences were in the higher heart rates of the miliaria group (A) and their higher NaCl concentration in sweat (Table II).

DISCUSSION

1. Factors affecting Sodium and Chloride Concentration in Sweat

The observed differences between miliaria subjects and controls appear to support the hypothesis which this experiment was designed to test. Nevertheless, certain possible sources of error must be considered; they comprise the following:

Salt Intake

As stated above, it is unlikely that group A had a higher intake of salt than the control groups. It should be remembered, too, that several of these chronic miliaria subjects had not been exposed to conditions of heat and humidity for many months before the experiment and would consequently have little cause to consume more than the average intake of salt. It does not seem, therefore, that the high concentration of salt in the sweat in group A could be attributed to an excessive salt intake, as reported by several writers.[7-12] It is also to be mentioned that under certain conditions the chloride concentration of human sweat does not rise with addition of salt to the drinking water,[13] or may actually fall.[14] A full list of references to work on the various factors that may influence the salt concentration in the sweat may be found in Robinson and Robinson;[11] the present-day view is expressed by Leithead,[15] who states: 'It is fairly clear from the work of several observers that changes in sweat chloride are related far more to the intake of salt than to acclimatization to heat'. We feel that this factor is not operative in our experiment.

Normal Values

There seems to be no unanimity on what constitutes the normal range of values for sodium and chloride concentrations in sweat. Robinson and Robinson[11] review the literature and mention values of 5 - 148 mEq./l. in supposedly normal subjects in hot environments; they add that average values of sweat chlorides ranging from 18 to 97 have been reported in at least 86 studies. Similar wide variations are summarized by Altman.[16] Some of the discrepancies are no doubt due to the fact that scarcely any two sets of experiments have been conducted under identical conditions; environmental temperature and humidity, sweat rate, state of work or rest, degree of acclimatization, and methods of sweat production, show wide variations. Thus the collection of sweat may have been performed as in our cases, or by encasing the whole or a part of the body in an impermeable bag, or by micropipette from the palmar sweat pores,[17] or from different areas of the body surface.[18]

In other investigations[19, 20] sweat produced by pilocarpine iontophoresis or mecholyl injection has been used to draw up a range of normal and abnormal values. As an example of the possible fallacies inherent in this diversity of experimental method, we refer to Weiner and Van Heyningen's statement[21] that sweat collected in an arm bag does not give the same results as total body sweat. Robinson and Robinson[11] have stated that values of 80 mEq./l. or more reported in the literature are most frequently found in samples collected from local skin areas enclosed in impermeable barriers. Where the skin is aerated and sweat residues efficiently washed off, sweat-chloride values rarely exceeded 60 mEq./l., even in unacclimatized men. The figures reported by Conn and co-workers[22, 23] (mean of 42 and range of 15 - 60 mEq./l.) were produced under his standard conditions of sweating and agree closely with our one-hour results for controls.

Although it is impossible to set precise limits to the normal range of concentration of sodium and chloride in sweat, we may nevertheless regard significant differences between our miliaria and control groups as important, so long as we make our comparisons between these groups and do not try to equate them with all supposedly normal values determined elsewhere. Our figures show that the greatest relative differences between groups are found at one hour and suggest that this measurement would in future suffice for similar investigations.

Effect of Age

Siegenthaler *et al.*[9] found that the concentration of sodium in sweat increased with age, averaging 32·6 mEq./l. between 20 and 25 years and 54·3 mEq./l. in subjects over 50. The scatter in each series (10 - 80 and 15 - 116), as well as the fact that use was made of pilocarpine iontophoresis, do not permit us to take these figures as standard values; they do however suggest that age might be a factor in salt concentration of sweat, however produced. In our own small series the age distribution between groups is reasonably close, and in none of the groups was there an observable relation between age and concentration of electrolytes.

State of Acclimatization

Judged on the usual criteria of acclimatization to heat—heart rate, temperature, sweat rate, and NaCl concentration in sweat—our subjects present an equivocal picture. Sweat rates and temperatures were not significantly different in the three groups. In the miliaria subjects the heart rates and NaCl concentration in the sweat and urine were raised. On these two criteria of acclimatization the miliaria group (A) could be regarded as relatively less well acclimatized (some of them had, of course, also been away from underground work for some months because of their medical condition). It must be stated that the lack of difference between the two control groups, one that had worked underground, the other that had not, was surprising. The degree of stress employed was not very severe, and this fact might have failed to differentiate between the groups in their state of acclimatization. A difference between acclimatized and unacclimatized men in heart rates, temperatures, and NaCl in sweat, is now well documented. It will, however, be observed that in our experiment there was no significant difference in the excretion of salt in the sweat of acclimatized and non-acclimatized controls (groups B and C); this agrees with Leithead's observation.[15]

Individual Variations

While there is no known inherent racial difference, several observers[7, 11] have stressed an individual factor in determining the concentration of electrolytes in sweat; according to Johnson *et al.*[14] such individual idiosyncracy is the central factor.

2. Sodium and Chloride Concentrations in the Sweat of Miliaria Subjects

The crucial question posed by our results is that of cause or effect. *Are the high sodium and chloride concentrations in group A an aetiological factor in, or are they the result of, miliaria?* The latter hypothesis has been assumed by a few previous workers who have measured chloride concentrations in miliaria subjects. Thus Ladell and co-workers,[24] in their classical work on disorders caused by heat, postulated that exhaustion of the sweat glands produced a high sweat chloride and that after miliaria 'the sweat is richer in chloride'.[10] We cannot gather whether miliaria subjects also had their sweat analyzed *before* developing the disease; if not, we have no means of deciding whether the chlorides were higher as the result of miliaria. An exception is possibly afforded[36] by a patient of Ladell's, in whom an attack of prickly heat was followed by a higher excretion of salt in the sweat and by evidence of delayed acclimatization. There was, however, no proof that these changes followed the attack of prickly heat; they could equally have been present, but not estimated, shortly before the attack. Horne and Mole[25, 26] thought a high intake of salt to be an aetiologic agent; with mild miliaria sweat chlorides were 'constant', but higher values were obtained in severe and relapsing miliaria. Of 7 patients in Cawnpore, chloride values decreased in those who recovered, but remained high in one who did not. In another paper[27] they state that high sweat chlorides persist for more than 2 months after recovery from anhidrotic heat exhaustion, a condition known to be the result of severe miliaria.

It should be noted here that several of the miliaria subjects in our group A had recovered many months previously, on ceasing underground work, and that the man showing the highest sweat concentrations at one hour (sodium 130, chloride 109 mEq./l.) had not been exposed to excessive heat and humidity for over 2 years.

If these high concentrations were in fact caused by exhaustion of the sweat glands, one would expect that the wastage of salt produced would be partly compensated for by a reduced excretion of salt in the urine. But we have shown (Tables II and III), on the contrary, that these *miliaria subjects excrete a significantly greater amount of sodium by this channel.* Interestingly, Ladell *et al.*[24] also found an increase in urinary chloride in their anhidrotic heat exhaustion cases, i.e. miliaria subjects. In our opinion, then, *the alteration in salt economy shown by group A is not the result of miliaria but more probably an aetiologic factor.* This would be in agreement with the hypothesis previously advanced.[1, 2] We do not, however, imply that a high concentration of salt in the sweat is the only, or even the most important, aetiologic factor, for two members of group B showed a concentration higher than the mean of group A after 4 hours' sweating; but, as previously stated, the results after 1 hour showed relatively low values in all.

If excessive salt excretion does in fact predispose certain subjects to the risk of miliaria, then it is pertinent to ask under what conditions such salt excretion could occur. Sargent[37] has recently listed some of the causes of altered chloride concentration in sweat; these are sweat rate, work rate, skin temperature, dietary intake, state of acclimatization, activity of the adrenal glands, and individual differences. We shall now consider two of these in detail.

Congenital

We have quoted Johnson *et al.*[14] as stating that an individual idiosyncracy is the central factor in determining the concentration of sodium in sweat. A possibly relevant fact is that parents and siblings of children with fibrocystic disease of the pancreas (mucoviscidosis) may show a high sweat sodium[19, 28] and there is some evidence that this may be associated with chronic endobronchial disease.[28, 29] We may mention in passing that a possible relationship to silica pneumoconiosis ('miners' phthisis') is being investigated. An attempt is also being made to investigate the families of sufferers from fibrocystic disease with regard

to their predisposition to miliaria. A fact we feel to be important is that sufferers from fibrocystic pancreatic disease show *low* sodium values in the urine.

Acquired

The only other known cause of high salt excretion in both sweat and urine is adrenal insufficiency.[8, 23, 29] Chronic heat stress has been mentioned as producing the general adaptation syndrome of Selye,[30] and particularly adrenal cortical hypofunction in the stage of exhaustion. If Selye's version is correct—that the so-called collagen diseases may be evoked by stress—it is interesting to recall that generalized systemic sclerosis has an extremely high incidence,[31] and that discoid lupus erythematosus frequently shows a florid pattern, in gold miners.[32]

The significantly higher heart rates of the miliaria cases could also be construed as a sign of an excessive cardiovascular reaction to stress. However, it is impossible to rule out completely the possibility that the higher heart rates and higher NaCl concentration in sweat of the miliaria subjects are due to a loss of acclimatization.

Horne and Mole[25] were apparently the first to suggest that miliaria might be a manifestation of some general metabolic disturbance; Sargent and Slutsky,[33] in a brilliant appraisal of all the facts available to them, then suggested that the seat of this metabolic disturbance was primarily in the pituitary-adrenal system.

Though the present paper is concerned with experimental rather than clinical findings, a single case history is so suggestive as to merit quotation:

A White miner, aged 40, and with 21 years' underground service, was brought to this hospital severely gassed with nitrous fumes after an underground explosion. He was critically ill for several weeks and was kept on therapy with corticosteroids for 3 months. When he returned to his former work, after passing tests for physical fitness, he developed extensive miliaria within three days, and has for some months continued to be unable to work underground without recurrences of miliaria. *He had never previously suffered from miliaria.*

Though Sargent and Slutsky[33] concluded that neuroendocrine factors were the cause of miliaria, they stated that sweat-gland fatigue was the keystone of this hypothesis. Our results suggest that, unless this is accompanied by renal tubular fatigue, the presence of simultaneous excess of salt in sweat and urine invalidates this hypothesis. We believe that adrenal cortical hypofunction—the word 'fatigue' might be applicable here—provides an adequate explanation of the observed phenomena. In agreement with Conn *et al.*[23] we regard the electrolyte content of thermal sweat as an index of adrenal cortical function; no intrinsic disorder of the sweat glands needs to be postulated. Shuster[34] has recently produced indirect evidence to confirm this conclusion, and has shown that aldosterone is responsible for the fall in sweat sodium on a low-sodium diet, and finally Conn[35] has shown that symptoms of loss of acclimatization are associated with diminished production of aldosterone or the administration of an aldosterone antagonist.

We feel, therefore, that chronic miliaria may be the end-result of a train of circumstances initiated by a loss of acclimatization.

SUMMARY

Physiological responses to 5 hours of moderate work in a heat chamber were studied in 10 sufferers from chronic miliaria and 12 control subjects. Six of the latter were acclimatized men, working under the conditions in which miliaria had been contracted by the 10 former.

The miliaria group showed a significantly higher concentration, and produced a significantly greater quantity, of salt in both sweat and urine. There is no evidence of a higher salt intake in this group.

The results obtained after 1 hour showed the greatest differences, and this time is regarded as the optimum for testing.

The findings support the hypothesis that increased concentrations of salt in the sweat are an aetiological factor in miliaria.

The possible causes of increased salt excretion, persisting for years after leaving the miliaria-producing environment, are discussed.

The state of acclimatization may be a factor in accounting for the observed differences. A significantly higher heart rate in the miliaria cases may be construed as a stress reaction.

Similarly, chronic miliaria may be regarded as a manifestation of stress.

REFERENCES

1. Loewenthal, L. J. A. (1961): Arch. Derm., **84**, 2.
2. *Idem* (1962): *Ibid.*, **86**, 455.
3. *Idem* (1962): Report on a journey to the Middle East and India, February 1962 (circulated privately).
4. Cotlove, E., Trantham, H. V. and Bowman, R. L. (1958): J. Lab. Clin. Med., **51**, 461.
5. Lingane, J. J. (1953): *Electroanalytical Chemistry*. New York: Interscience Publishers.
6. King, E. J. and Wootton, I. D. P. (1956): *Micro-Analysis in Medical Biochemistry*, pp. 193-196. London: Churchill.
7. Adolph, E. F. (1947): *Physiology of Man in the Desert*. New York: Interscience Publishers.
8. Conn, J. W. (1949): Advanc. Intern. Med., **3**, 373.
9. Correspondence (1962): Lancet, **1**, 538.
10. Ladell, W. S. S. (1957): Trans. Roy. Soc. Trop. Med. Hyg., **51**, 189.
11. Robinson, S. and Robinson, A. H. (1954): Physiol. Rev., **34**, 202.
12. Robinson, S., Kincaid, R. K. and Rhamy, R. K. (1950): J. Appl. Physiol., **3**, 55.
13. Kawahata, A. (1950): Mie Med. J., **1**, 123.
14. Johnson, R. E., Pitts, G. C. and Consolazio, F. C. (1944): Amer. J. Physiol., **141**, 575.
15. Leithead, C. S. (1962): Personal communication.
16. Altman, P. L. *in* Dittmar, D. S. ed. (1961): *Blood and other Body Fluids*. Washington, DC: Federation of American Societies for Experimental Biology.
17. Lobitz, W. C. and Osterberg, A. E. (1947): Arch. Derm. Syph. (Chic.), **56**, 462.
18. Mickelsen, O. and Keys, A. (1953): J. Biol. Chem., **149**, 479.
19. McKendrick, T. (1962): Lancet, **1**, 183.
20. Schwartz, I. L. and Thaysen, H. J. (1956): J. Clin. Invest., **35**, 144.
21. Weimer, J. S. and Van Heyningen, R. E. (1952): Brit. J. Industr. Med., **9**, 56.
22. Conn, J. W. (1949): Arch. Intern. Med., **83**, 416.
23. Conn, J. W., Louis, L. H., Johnston, M. W. and Johnson, B. J. (1948): J. Clin. Invest., **27**, 529.
24. Ladell, W. S. S., Waterlow, J. C. and Hudson, M. F. (1944): Lancet, **2**, 491 and 527.
25. Horne, G. O. and Mole, R. H. (1949): *Ibid.*, **2**, 279.
26. *Idem* (1951): Trans. Roy. Soc. Trop. Med. Hyg., **45**, 79.
27. *Idem* (1950): *Ibid.*, **44**, 193.
28. Wood, J. A., Fishman, A. P., Reemtsma, K., Barker, H. G. and Di Sant' Agnese, P. A. (1959): New Engl. J. Med., **260**, 951.
29. Peterson, E. M. (1959): J. Amer. Med. Assoc., **171**, 1.
30. Selye, H. (1950): *Stress*. Montreal: Acta Inc.
31. Erasmus, L. D. (1957): S. Afr. J. Lab. Clin. Med., **3**, 209.
32. Loewenthal, L. J. A. *in* McLean, E. M. ed. (1964): *Mine Medical Officers' Manual* (in the press).
33. Sargent, F. and Slutsky, H. L. (1957): New Engl. J. Med., **256**, 401 and 451.
34. Shuster, S. (1962): Proc. Roy. Soc. Med., **55**, 719.
35. Conn, J. W. (1963): J. Amer. Med. Assoc., **183**, 775.
36. Ladell, W. S. S. (1951): Brit. Med. J., **1**, 1358.
37. Sargent, F. *in* Montagna, W., Ellis, R. A. and Silver, A. F. eds. (1962): *Advances in Biology*, vol. III, p. 185. London: Pergamon Press.