argued that the three-day trial is not adequate and that more prolonged hormone administration would iron out these differences, but in the seven cases given more prolonged courses the degree of responsiveness did not seem to alter greatly, though there was a tendency for the more responsive patients to become somewhat less so.

A number of practical points arise from these observations. Thus the individual patient's responsiveness to cortisone and A.C.T.H. should be considered before embarking upon any programme of treatment with these hormones. and we suggest that the single-dose test may give a useful indication of this, though the three-day test would be more reliable. Furthermore, it seems unwise to state that a given syndrome in a given patient is unaffected by cortisone or A.C.T.H. unless enough hormone has been administered to produce signs of hypercorticism: a procedure not without danger. It is also clearly essential to assess the individual patient's responsiveness with cortisone or A.C.T.H. of known potency before attempting to assess the presence of similar activity in other substances or preparations by administering them to patients.

One of the most interesting findings in our series was the withdrawal deterioration which was sometimes observed in cases in which the administered hormone had no apparent effect, as in Cases 7, 9, and 10. According to Sayers (1950), tissue requirements of corticosteroids are greatly increased during stress, and the pituitary–adrenocortical system responds to these increased requirements by increased production of steroids, so maintaining a state of eucorticism; and no convincing evidence has as yet been produced to show that this mechanism is not working normally in rheumatoid disease. Although the response to cortisone or A.C.T.H. must be determined by many factors, such as the rates of absorption and destruction of the administered hormones, the degree of tissue responsiveness, tissue requirements, and so on, we suggest that the differing response of individual patients to administered cortisone and A.C.T.H. may be partly a reflection of the level of endogenous production. If the administered dose of hormone greatly exceeds endogenous production it causes some degree of hypercorticism, with eosinopenia and suppression of the inflammatory reaction, resulting in a clinical response; but if the administered dose is less than the amount produced endogenously the pituitary–adrenocortical system merely adjusts itself to a lower level of production and the net result is no change, though there may be a temporary withdrawal deterioration while endogenous production is getting under way again. Investigation of this hypothesis must, however, await accurate methods of assessing corticosteroid production in conditions of disease in which "utilization" is presumably high.

Although Hench and his colleagues (Ward *et al.*, 1951) and other workers (Boland and Headley, 1951; Copeman *et al.*, 1952) claim satisfactory results with prolonged cortisone therapy in selected cases of rheumatoid arthritis, other workers (Freyberg *et al.*, 1951) are less enthusiastic, and from Duthie's (1952) review of up-to-date American experience it seems that such long-term therapy is unsatisfactory in most patients with rheumatoid disease. If we are not in fact restoring a state of eucorticism in the rheumatoid patient by administering a "clinically adequate" dosage of cortisone or A.C.T.H. but are merely producing a partial suppression of the inflammatory reaction by inducing a more or less subclinical state of hypercorticism, one would hardly expect the results to be uniformly good, and our own limited experience is certainly not encouraging. The proper evaluation of long-term cortisone or A.C.T.H. therapy in rheumatoid disease must, however, await the completion of controlled therapeutic trials.

Summary

Seventeen patients with rheumatoid arthritis were given standard three-day courses of 600 mg. of cortisone and 300 mg. of A.C.T.H. and their clinical and eosinopenic responses were studied in detail.

Four patients responded fully to both hormones, four gave no response with either hormone, four responded fully to cortisone but only partially or not at all to A.C.T.H., while one responded fully to A.C.T.H. and only partially to cortisone. The remainder gave only partial responses to either or both hormones.

The practical and theoretical implications of these findings are discussed, and it is suggested that the degree of response to a standard dose may to some extent be a reflection of the level of endogenous production.

The cortisone used in this work was provided from a generous gift made jointly to the Nuffield Foundation and the Medical Research Council by Merck and Co., Inc., and the A.C.T.H. was supplied by the Medical Research Council and Organon Laboratories Ltd.

REFERENCES

Bassil, G. T., and Hain, A. M. (1950). *Nature, Lond.*, **165**, 525.
Boland, E. W., and Headley, N. E. (1951). *J. Amer. med. Ass.*, **145**, 8.
Copeman, W. S. C., Savage, O., Bishop, P. M. F., Dodds, E. C., Kellie, A. E., Stewart, J. W., Glyn, J. H. H., Henly, A. A., and Tweed, J. M. (1952). *British Medical Journal*, **1**, 397.
Duthie, J. J. R. (1952). Ibid., **1**, 341.
Freyberg, R. H., Traeger, C. H., Patterson, M., Squires, W., Adams, C. H., and Stevenson, C. (1951). *J. Amer. med. Ass.*, **147**, 1538.
Janus, O. (1950). *British Medical Journal*, **2**, 1244.
Kellgren, J. H., and Janus, O. (1951). Ibid., **2**, 1183.
Marrian, G. F. (1951). *J. Endocrinol.*, **7**, lxix.
Robinson, A. M., and Norton, J. M. (1951). Ibid., **7**, 321.
Sayers, G. (1950). *Physiol. Rev.*, **30**, 241.
Ward, L. E., Slocumb, C. H., Polley, H. F., Lowman, E. W., and Hench, P. S. (1951). *Proc. Mayo Clin.*, **26**, 361.

EFFECT OF REPEATED INJECTIONS OF A.C.T.H. UPON THE BONE MARROW

BY

G. HUDSON, M.B., Ch.B., B.Sc.
Demonstrator in Anatomy

G. HERDAN, M.Sc., Ph.D., LL.D.
Lecturer in Statistics, Department of Preventive Medicine

AND

J. M. YOFFEY, M.D., D.Sc., F.R.C.S.
Professor of Anatomy
University of Bristol

In a previous paper (Yoffey *et al.*, 1951) the effects of a single administration of A.C.T.H. or of cortical extract ("eschatin") upon the bone marrow were reported. For the examination of the marrow a quantitative method was employed, and attention was directed more especially to the lymphocytes. It was then found that six hours after a single dose of eschatin a statistically significant increase occurred in the marrow lymphocytes, while six hours after a single injection of A.C.T.H. there was an increase in the marrow lymphocytes which almost reached significance level. Following these experiments it was thought that perhaps repeated administration of A.C.T.H. might produce a more decisive change in the marrow lymphocytes. Accordingly a number of guinea-pigs were given daily injections of A.C.T.H. for seven days, and the marrow was then examined. While these experiments have not yielded much further information about the marrow lymphocytes, they have served to direct attention to a possible stimulating action of A.C.T.H. on the bone marrow as a whole, and especially on erythropoiesis.

Material and Technique

The work was done throughout on normal guinea-pigs of the Mill Hill strain originated by Dunklin and Hartley. Healthy animals about 4–6 months old were obtained from the University of Bristol Veterinary Field Station at Langford through the kindness of Professor Blakemore.

Seven normal guinea-pigs, after having a blood count taken from an ear vein, were killed and the bone marrow examined. In nine other guinea-pigs a blood count was taken and the animals were given daily injections of A.C.T.H. for seven days, after which another blood count was made, the animals were killed, and the bone marrow was removed for examination.

Both absolute and differential blood counts were made, using Wright's stain and water at *p*H 6. Eosinophil counts were performed by a modification of Randolph's method, the diluent being a mixture of equal parts of propylene glycol and 0.05% phloxine in water. Reticulocytes were counted by the brilliant-cresyl-blue method—1% in absolute alcohol allowed to dry on the slide. As a rule the entire examination of the blood required four to five drops, and sometimes a little more than this may have escaped; but in experiments 19, 20, and 22 care was taken not to withdraw more than three small drops.

For the marrow counts we employed the quantitative technique previously described (Yoffey *et al.*, 1951). The animals were killed by exsanguination under ether anaesthesia. A humerus was then removed and cleaned, the ends were sawn off, and marrow was ejected by a rubber tube and blower into a small corked glass tube containing human plasma. The weight of both the tube and the plasma being known, the weight of the bone marrow could be ascertained. The dilution could be calculated by using a correction factor previously determined from measurements of the specific gravity of 12 samples of bone marrow and plasma. The marrow was shaken for three minutes in a mechanical shaker at 400 times a minute, and usually an even suspension of cells could be obtained, from which counts could be made and smears prepared in the usual manner. If the suspension showed many cell clumps the experiment was discarded. Besides the total content of nucleated cells, red blood cells in the marrow suspension were counted as well as the reticulocytes, again using in the case of the latter the same brilliant cresyl-blue technique. Eosinophils in bone marrow were counted by the method already described for blood. Marrow smears were stained by Wright's stain diluted with water at *p*H 6. In the differential count 400 cells were counted.

Three different preparations of A.C.T.H. were used. In experiments 5, 7, and 8 we used A.C.T.H., kindly supplied by Dr. W. O. Reinhardt and Dr. C. H. Li, of California. The batch number was 20760, and an assay by Sayers's method in hypophysectomized rats, in dose levels of 5 γ per 100 g. rat body weight, gave reductions in mg. of ascorbic acid per 100 g. of adrenal of −178, −178, and −132. This was dissolved in 0.9% saline containing 0.001/N HCl and a sterile solution was injected intraperitoneally, 1 mg. of A.C.T.H. in 0.3 ml. daily for seven days. In experiments 10, 12, 13, and 16 a lyophilized A.C.T.H. powder was used, also supplied by Drs. Reinhardt and Li. It was recommended that this be dissolved in 0.001/N HCl, in a boiling-water bath for one hour. The solution was then neutralized to *p*H 3, which was satisfactory for injections. In the remaining experiments A.C.T.H. (Armour) was employed; for this we are indebted to the Medical Research Council.

At the end of a week's injection of A.C.T.H. and 24 hours after the last injection, another full blood count was performed. From the dead animal not only was bone marrow examined by the method noted, but smears of teased lymph nodes (mesenteric) suspended in plasma were also stained (Wright's) and examined, both to observe possible changes in the lymphocytes and to facilitate identification of these cells in the marrow smears.

Results

Table I presents the main data of the seven experiments on normal guinea-pigs, and Table II those of the nine A.C.T.H. experiments.

In comparing these results with those of the first series of experiments, in which only one injection of A.C.T.H. was given, the essential fact emerges that in the present instance the total count of the nucleated cells of the bone marrow has risen significantly from 1,248,000 to 1,705,000 per c.mm. In consequence, the results in absolute numbers and percentages need no longer run parallel, so that a significant rise in the absolute count of a certain type of cell need not be accompanied by a similar rise in percentage.

1. *Myeloid Cells.*—Tables I and II are based upon the differential counts performed upon smears stained with Wright's stain. In these it was not always possible to differentiate marrow eosinophils from neutrophils. The latter cells in the guinea-pig—as in several other mammals—are rather more eosinophilic in their staining reactions than human neutrophils; accordingly, although in every case the attempt was made to distinguish in smears between eosinophils and neutrophils (pseudo-eosinophils or heterophils), it was felt that the most reliable indication of eosinophil changes was to be found in the propylene glycol counts. Fuller details of the differential counts of the various granular cells will be presented elsewhere. In the present communication the "myeloid" column in Tables I and II includes all the granular cells of the marrow—namely, neutrophils, eosinophils, and the occasional basophil cell. It will be noted from Table III that the total myeloid cells show a significant rise in the average absolute count from 326,320 in the control series to 523,550 in the experimental series without a corresponding significant change in average percentage, which increased from 27 to 29.72. The aver-

TABLE I.—*Marrow Counts in Seven Normal Guinea-pigs*

Serial No. of Expmts.		Erythroid	Myeloid	Lymphocytes	Monocytes	Damaged	Unclassified	Total Absolute Count	M:E Ratio
3	%	12·25	23·75	15·0	3·5	40·75	3·5	2,120,000	1·94
	Absolute	259,400	501,800	317,900	74,000	864,000	74,000		
4	%	12·25	42·25	12·75	11·75	15·0	7·25	959,000	3·45
	Absolute	117,500	405,200	122,000	112,700	143,800	69,300		
6	%	14·0	23·0	25·5	9·0	22·0	6·0	1,046,000	1·64
	Absolute	146,400	240,600	266,700	94,100	230,100	62,700		
9	%	11·75	29·0	17·0	4·25	31·0	5·75	977,000	2·47
	Absolute	114,800	283,300	166,100	41,500	305,600	56,200		
11	%	13·25	24·5	19·5	11·0	27·25	4·0	1,058,000	1·85
	Absolute	129,600	259,100	203,500	116,350	288,200	42,300		
15	%	19·0	26·5	32·0	4·5	15·0	1·75	1,221,000	1·4
	Absolute	231,800	323,300	390,500	55,000	183,100	22,400		
21	%	28·75	20·0	19·0	10·25	17·0	4·5	1,355,000	0·7
	Absolute	389,600	271,000	257,300	138,900	230,300	57,580		

All absolute counts are in cells per c.mm. of marrow.

TABLE II.—*Marrow Counts in Nine Guinea-pigs which had been given Daily Injections of 1 mg. of A.C.T.H. for Seven Days*

Serial No. of Expmts.		Erythroid	Myeloid	Lymphocytes	Monocytes	Damaged	Unclassified	Total Absolute Count of Nucleated Cells	M:E Ratio
5	%	6·75	31·0	33·0	5·5	16·25	5·15	1,900,000	4·7
	Absolute	128,200	598,200	627,000	104,500	308,600	104,500		
8	%	31·25	27·5	13·0	5·75	13·75	7·25	1,818,000	0·88
	Absolute	568,200	499,700	236,200	104,600	249,800	131,800		
10	%	34·25	34·25	13·0	2·0	12·25	3·75	1,700,000	1·0
	Absolute	582,000	582,000	221,000	34,000	208,200	63,700		
12	%	27·25	33·75	11·0	5·0	14·0	7·0	1,882,000	1·24
	Absolute	506,300	634,300	206,800	94,000	263,300	131,700		
13	%	26·5	28·0	11·0	7·75	19·5	5·25	1,558,000	1·06
	Absolute	412,500	436,000	171,200	120,800	304,000	81,700		
16	%	18·0	20·5	20·5	6·25	29·0	4·0	1,498,000	1·14
	Absolute	269,600	307,000	307,000	94,180	434,400	59,900		
17	%	26·25	38·0	7·5	4·0	15·0	7·25	1,606,000	1·45
	Absolute	423,000	610,000	120,000	64,200	240,800	116,000		
19	%	22·5	17·75	21·5	10·5	22·5	5·0	1,560,000	0·79
	Absolute	351,000	276,800	335,200	163,800	35,000	78,000		
20	%	24·0	36·75	2·75	10·75	20·25	4·25	1,815,000	1·53
	Absolute	435,300	677,100	49,900	195,000	367,200	77,100		

All absolute counts are in cells per c.mm. of marrow.

age eosinophil count (propylene glycol) rose from 43,900 to 69,620; this increase did not reach significance level. It is of interest in this connexion that neither did the blood eosinophils show a significant change in the experimental animals.

2. *Lymphocytes.*—The lymphocytes show a percentage drop from 20.1 in the normals to 13.56 in the experimental series. This difference does not reach significance level. The average absolute count shows a small rise (246,000 to 252,700), and this again is not significant. The drop in the percentage is evidently produced by the increase in the total nucleated cell count, while the absolute number of lymphocytes has remained more or less the same. The identification of the small lymphocyte has presented the same problems as previously discussed (Yoffey *et al.*, 1951). In the present experiments with A.C.T.H. there appeared at times to be an increased number of lymphocytes with varying degrees of leptochromasia, which could be interpreted as transitional forms between small lymphocytes and micromyeloblasts.

3. *Damaged Cells.*—These show a drop from 24% to 17.11%, which, though not big enough to reach the conventional significance level, has a fairly small probability of being due to pure chance (somewhat less than 10%).

4. *Erythroid Cells.*—In the case of the erythroid cells there is a significant rise in the experimental series both in percentage (15.89 to 24.1) and in absolute numbers (198,400 to 408,450). The marrow reticulocytes have also risen significantly, from 68,150 in the controls to 108,720 in the experimental animals. It is interesting also that the total number of red blood cells in the marrow suspension has risen significantly, from 1,741,400 to 2,234,100. So far as the red cells of the blood are concerned, the reticulocytes did show a significant increase from 1.01% to 1.85%.

Table III summarizes the essential features of the above observations.

TABLE III.—*Comparison of Absolute and Percentage Counts of Different Types of Nucleated Cells, Reticulocytes, and M:E Ratio in the Marrow of Seven Control Animals and Nine Animals which were Given Seven Daily Injections of A.C.T.H. Absolute Counts are in Cells per c.mm. of Marrow. Percentage Counts are of the Total Nucleated Cells*

	Control Series	Experimental Series	Change
Erythroid cells	198,400	408,450	S
	15·89%	24·1%	S
Myeloid cells	326,320	523,550	S
	27%	29·72%	N
Lymphocytes	246,280	253,700	N
	20·1%	13·56%	D
Damaged cells	320,720	267,920	D
	24%	17·11%	D
M/E ratio	1·92	1·52	N
Total absolute count	1,248,000	1,704,100	S
Eosinophils	43,900	69,620	N
Reticulocytes	66,150	108,720	S
Red blood cells	1,741,400	2,234,100	S

S = Significant increase according to the t-function. D = Diminution not quite reaching significance level. N = No significant change.

Discussion

The results may not be quite as clear-cut as they at first sight appear. In these attempts to apply quantitative methods to the study of bone marrow a completely satisfactory technique has not yet been evolved. One of the most difficult problems has been to obtain a uniform distribution of cells and at the same time to ensure that the individual cells are spread out sufficiently to facilitate the observation of structural detail and so make accurate identification possible. Slowly made smears are thinner, with a better spread of individual cells, but they have two serious defects: more cells are damaged and the larger cells concentrate at the edges. In rapidly made smears, on the other hand, the distribution of the cells is more even and fewer are damaged, but the individual cells are not so well spread, so that they are shrunken and rounded off, thus rendering cell identification difficult, if not impossible. Supravital studies which are now being made should obviate these difficulties, but may introduce other problems in connexion with cell identification.

Subject to limitations of this kind, the results suggest the possibility that A.C.T.H. may act as a stimulus to the bone marrow as a whole, but more especially to the erythroid series. It has already been noted that, associated with the increased erythropoietic activity of the bone marrow during the experimental period, the blood reticulocytes also showed a definite increase. Taken in conjunction, the marrow and blood findings would suggest that if the A.C.T.H. administration were continued for a sufficient length of time an actual polycythaemia could conceivably develop. A change of this kind has in fact been described in the mouse (White and Dougherty, 1945) after comparatively enormous doses of A.C.T.H., though not in rats (Palmer *et al.*, 1951). Presumably also, in cases of Cushing's syndrome (Wintrobe, 1951), it is the excessive production of endogenous A.C.T.H. which is responsible for the not infrequent development of polycythaemia. On the other hand, if endogenous A.C.T.H. is secreted in diminishing amounts, erythropoiesis is correspondingly depressed. Hence the varying degrees of anaemia which are associated with hypopituitarism (Summers and Sheehan, 1951). However, whether from the point of view of hyperpituitarism or hypopituitarism, it would seem that there must be some sort of limiting factor in the mechanism whereby an effect on erythropoiesis is produced; for a steadily progressive polycythaemia does not usually develop

in hyperpituitarism of the appropriate type, nor does anaemia of increasing severity usually supervene in cases of marked hypopituitarism.

If A.C.T.H. really is capable of acting as an erythropoietic stimulus, what is its precise mode of action? Presumably it operates through the suprarenal cortex. This, at any rate, seems to have been generally assumed without question, though recent observations suggest that, on occasion, A.C.T.H. may exert its effect without the mediation of the suprarenals. Thus it has been reported (Palmer *et al.*, 1951) that A.C.T.H. may give rise to neutrophilia in rats even in the absence of the suprarenals. Similarly, Ralli (1950) noted that A.C.T.H. had a lymphocytopenic effect in adrenalectomized rats, the effect being conditioned by the pantothenate content of the diet. The possibility of a direct effect of A.C.T.H. on target organs raises a number of questions. There is, for instance, the likelihood of occasional contamination with growth hormone; in the present work control experiments with growth hormone were not performed.

Lowenstein *et al.* (1951) have reported that A.C.T.H. may constitute an appreciable erythropoietic stimulus in pernicious anaemia, and in one case they noted in the bone marrow a marked diminution of megaloblasts with a corresponding increase in normoblasts. Whether in these cases A.C.T.H. introduces a direct erythropoietic factor or acts more indirectly through its metabolic effects it is difficult to say. The complex series of changes which A.C.T.H. initiates introduces a large number of factors, any one of which, alone or in combination with others, may be responsible for some of the observed results. In the present instance it does not seem likely that there should be two completely different sources of anti-pernicious-anaemia factor, or two completely different anti-pernicious-anaemia factors with the same effect. A more plausible hypothesis would be that the liver upheavals associated with repeated administration of A.C.T.H. might somehow facilitate the liberation of an anti-pernicious-anaemia factor which would otherwise be too firmly bound in the liver.

It has of course been realized for a number of years that an increase in reticulocytes does not necessarily imply a steady and progressive increase in erythropoiesis. Minot and Castle (1935) showed that arsenic and protein derivatives could bring about a somewhat irregular reticulocytosis without effective increase in red-cell formation. The question of a non-specific reticulocytosis is a difficult one, and has recently been discussed by Plum (1949) (see also Wintrobe *et al.*, 1951). In the present work no attempt has been made to grade the reticulocytes in order of maturity, nor have we endeavoured to correlate changes in the reticulocytes with any alteration in the "ripening index" (Plum, 1949). Had the reticulocytes alone been found to be increased in the present experiments the change might well have been attributed to the non-specific action of a protein or other substance, with the further possibility that even here one might be dealing with a non-specific stress response involving the pituitary and suprarenal cortex. The marked increase in all the erythroid cells, and also the increased cellularity of the marrow as a whole, suggest something more than simply the disturbance of the final stages of red-cell maturation. The differential count of the erythroid cells in the marrow showed also not only the reticulocyte increase already mentioned, but a clear increase in proerythroblasts and polychromatic erythroblasts; the evidence therefore suggests an erythropoietic impetus all along the line (see also Irons *et al.*, 1951).

Little further light has been thrown in these experiments on the response of lymphocytes—and lymphoid tissue—to A.C.T.H. As compared with the previous series of experiments (Yoffey *et al.*, 1951), it should perhaps be noted that in the normal animals the lymphocyte content of the marrow was considerably higher. This difference we are unable to explain, but, whatever the reason, a high marrow lymphocyte count at the outset should have facilitated the detection of any subsequent lymphocytolytic action of A.C.T.H. In fact, there was a slight increase in the absolute numbers of the marrow lymphocytes, though a fall in their percentage, in neither case significant. Again, as in the earlier experiments, there was not only no increase in the number of damaged cells after prolonged administration of A.C.T.H., but an actual diminution. Neither of these findings appears to support the concept of increased lymphocyte breakdown.

Summary

In nine normal healthy guinea-pigs, which were given intraperitoneal injections of A.C.T.H. once a day for seven days, the marrow as a whole appeared to show increased cellularity, while there was also an increase in the number of myeloid and erythroid cells. There were no significant changes in the marrow lymphocytes.

It seems possible that A.C.T.H., either directly or indirectly, may stimulate the formation of new cells in the bone marrow.

ADDENDUM.—After this paper had been written and sent to the *British Medical Journal* we read the article by Quittner, Wald, Sussman, and Antopol ("The Effect of Massive Doses of Cortisone on the Peripheral Blood and Bone Marrow of the Mouse," *Blood*, 1951, **6**, 513), in which it is suggested that the effect of a single dose of cortisone is somehow to block the escape of myeloid cells from the bone marrow to the blood. This was accompanied by an increase in the M/E ratio.

It is a pleasure to acknowledge once again our indebtedness to Dr. G. H. Tovey, of the Blood Transfusion Centre, for providing us with regular supplies of oxalated plasma; to Miss L. Lloyd for assistance in the preparation of the manuscript; and to Mr. Alvan Barnes for his technical help.

REFERENCES

Irons, E. N., Ayer, J. P., Brown, R. G., and Armstrong, S. H. (1951). *J. Amer. med. Ass.*, **145**, 861.
Lowenstein, L., Shapiro, L., and Browne, J. S. L. (1951). *Proceedings of the Second Clinical A.C.T.H. Conference*, **1**, 426. Churchill, London.
Minot, G. R., and Castle, W. B. (1935). *Lancet*, **2**, 319.
Palmer, J. G., Cartwright, C. E., and Wintrobe, M. M. (1951). *Proceedings of the Second Clinical A.C.T.H. Conference*, **1**, 438. Churchill, London.
Plum, C. M. (1949). *Acta haemat., Basel*, **2**, 317.
Ralli, Elaine P. (1950). "*Adrenal Cortex*" *Transactions of the First Conference*, p. 159. Josiah Macy, jun., Foundation, New York.
Summers, V. K., and Sheehan, H. L. (1951). *British Medical Journal*, **2**, 564.
White, A., and Dougherty, T. F. (1945). *Endocrinology*, **36**, 16.
Wintrobe, M. M. (1951). *Clinical Hematology*, 3rd ed. Kimpton, London.
—— Cartwright, G. E., Palmer, J. G., Kuhns, W. J., and Samuels, L. T. (1951). *Arch. intern. Med.*, **88**, 310.
Yoffey, J. M., Metcalf, W. K., Herdan, G., and Nairn, Valerie (1951). *British Medical Journal*, **1**, 660.

The centenary of the birth of William Stewart Halsted, which falls on September 23, is to be celebrated at a meeting of the Section of Surgery of the Royal Society of Medicine on May 20, for which Dr. Alfred Blalock, Halsted's present successor in the Johns Hopkins chair of surgery, and Dr. S. J. Crowe, one of his former associates, are making a special visit to England. Halsted, a great surgical technician, was one of the pioneers of modern surgery in America. In 1892 he became the first professor of surgery at Johns Hopkins University and remained there for the rest of his life. In addition to introducing rubber gloves into the operating-room (1890), he was among the first to use silk sutures (about 1882). The first experiments on infiltration analgesia, using cocaine, were reported by Halsted in 1885. He introduced his method of radical mastectomy in 1882. Ten years later he was the first successfully to ligate the first part of the left subclavian artery, excising a subclavian aneurysm at the same time; this operation had been performed unsuccessfully four times before. (The first successful operation in Britain was carried out by Stonham in 1899, and the patient was demonstrated at the Royal Society of Medicine 22 years later.) Halsted's operation for the radical cure of hernia (1890) was a modification of Bassini's operation. He was also the first in America to drain the common bile duct, and his work on the thyroid and parathyroid glands is worthy of mention. His operative experience was stupendous, his method patient and careful. Halsted died in 1922.