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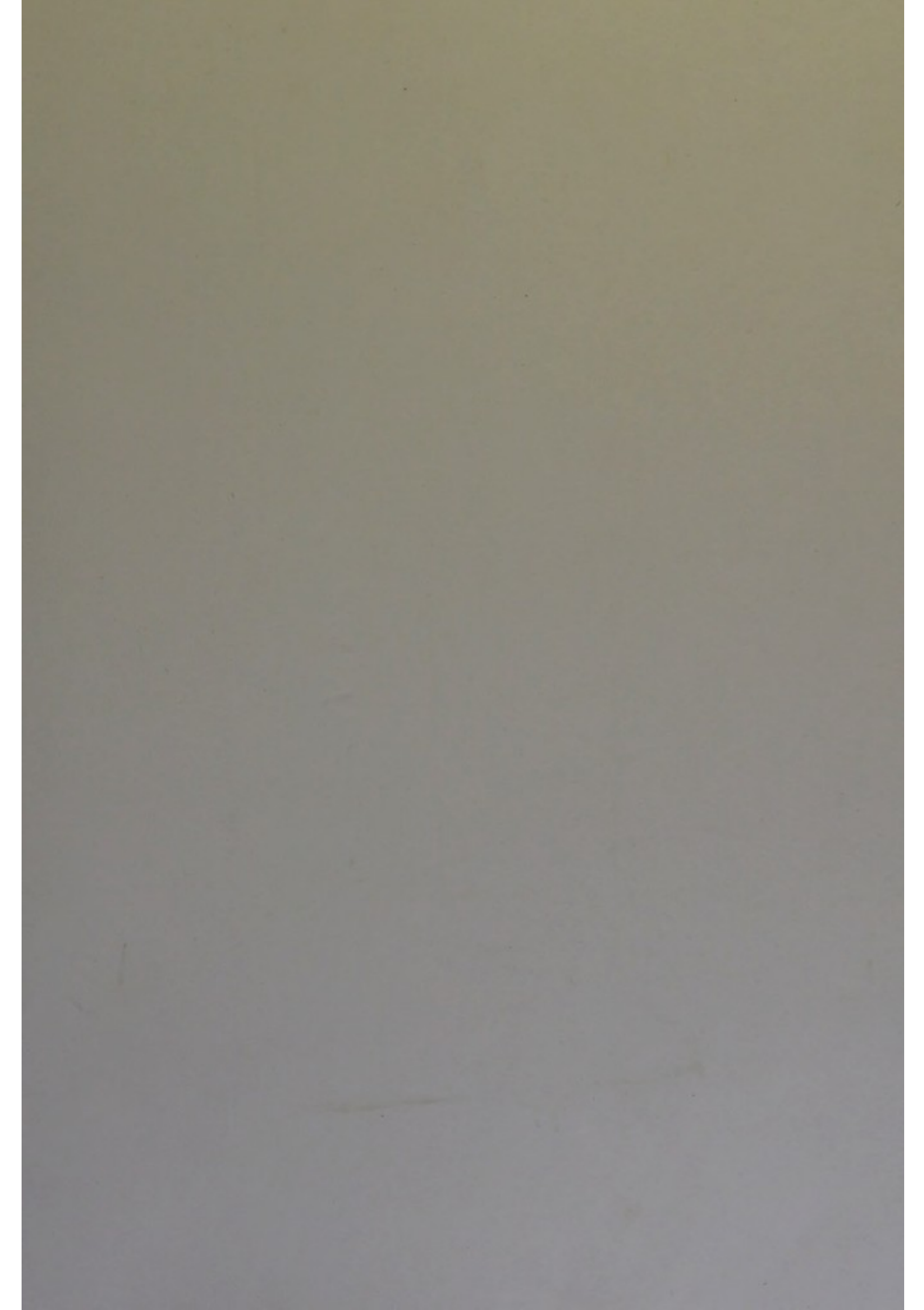
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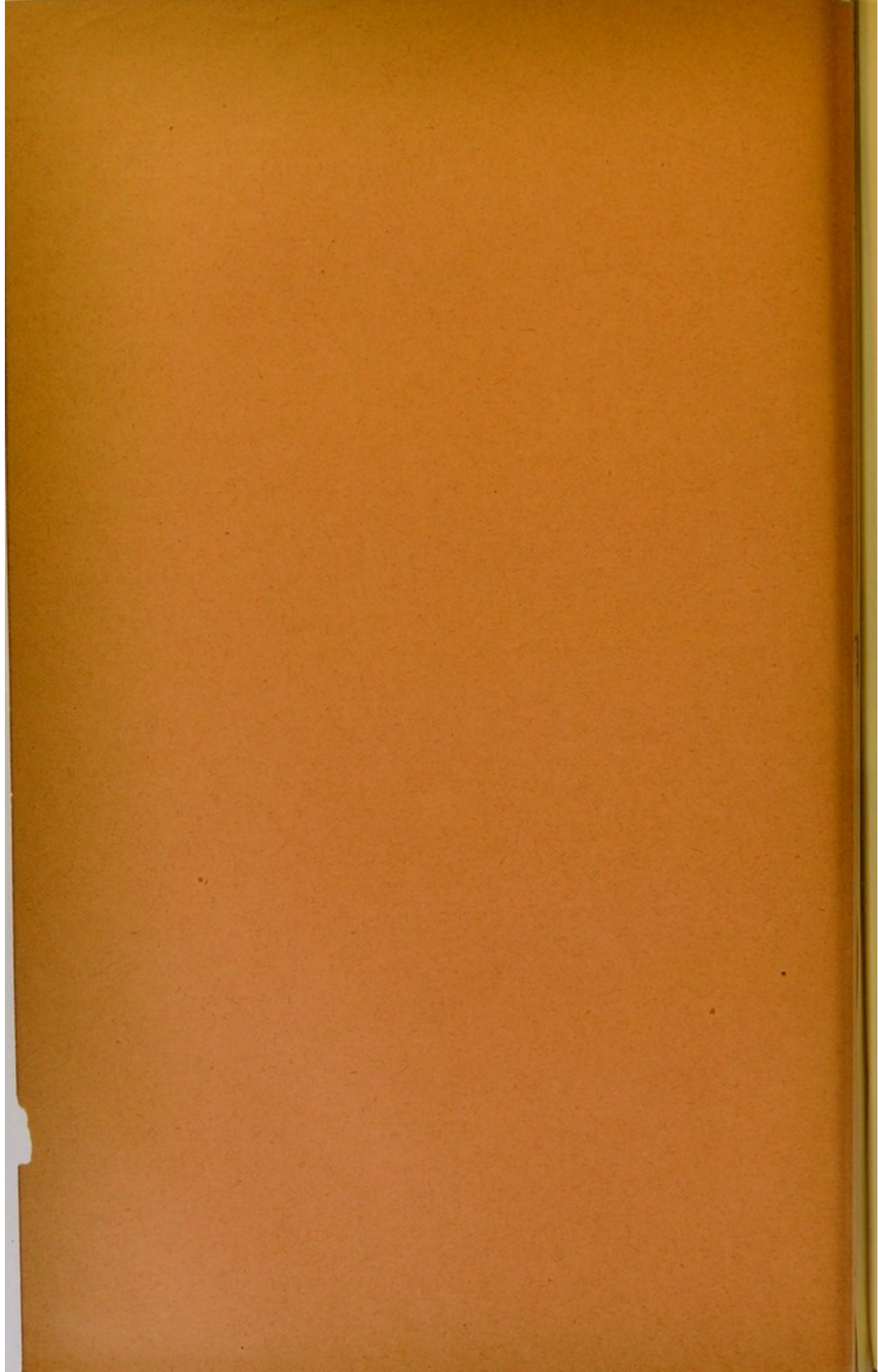
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AND BLOOD. BY RALPH STOCKMAN, M.D., F.R.C.P.E.
AND E. D. W. GREIG, M.B. Plate V.

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5



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THE ACTION OF ARSENIC ON THE BONE-MARROW
AND BLOOD¹. BY RALPH STOCKMAN, M.D., F.R.C.P.E.,
Professor of Materia Medica, University of Glasgow, AND E. D.
W. GREIG, M.B., *Assistant to the Professor of Pathology,*
University College, London. (Plate V.)

(*From the Laboratory of the Royal College of Physicians
of Edinburgh.*)

ARSENIC is known to have a remarkable effect in increasing the number of red blood corpuscles in some cases of pernicious anæmia, of leukæmia, and of lymphadenoma, although not infrequently in these diseases the blood condition is not perceptibly improved by its administration. In malarial anæmia also its hæmatinic value cannot be doubted, although its mode of action remains obscure. In chlorotic anæmia it is very commonly given along with iron in the belief that it hastens and improves corpuscle formation, yet cases treated with arsenic *alone* do not show any signs of improvement in the blood condition or otherwise². In health also it is incapable of increasing the number of red corpuscles above the physiological maximum, but this is equally true of all other tonic or dietetic measures, and *à priori*, therefore, one would not expect it to do so. So far as we have been able to discover, no experimental or other attempt has been made to explain the effects of arsenic on blood-corpuscle formation in those diseases in which it has proved of value clinically, and it was in the hope of obtaining some information in this direction that we undertook the present research. Our observations were made on young and adult rabbits, and on young dogs, the arsenic being given in small doses over long periods.

¹ The expenses of this research were defrayed by a grant from the British Medical Association.

² Cp. Stockman, *B. M. J.*, 1893.

Observations on Rabbits.

Five young healthy rabbits were taken from the same litter, and when they were between three and four weeks old, arsenic in small doses was administered daily to three of them, while the other two were kept for purposes of comparison. A 1 per cent. solution of arsenious acid made up with water and sodium carbonate was used, so that actually arsenite of sodium was the form in which it was administered. The solution was given hypodermically. The blood was examined almost daily with the Thoma-Zeiss hæmacytometer and von Fleischl's hæmoglobinometer.

OBSERVATION I. Duration 68 days.

Days	1—8.	Control of blood examination. During this time the red corpuscles were found to range between 5,397,000 and 5,712,000 per cub. mm. The hæmoglobin kept constant at 60 per cent.
„	9—20.	1/50 grain arsenious acid daily.
„	20—25.	1/33 „ „
„	26—37.	1/25 „ „
„	38—42.	1/16—1/11 „ „
„	43—68.	1/10 „ „

On the 68th day it showed symptoms of paralysis (apparently from arsenical neuritis) and was killed. It had remained up to this time in perfect health, and its weight had increased from 535 to 840 grms. In the same time the weight of the control rabbit had risen from 370 to 800 grms., while its blood remained practically constant as regards corpuscles and hæmoglobin.

During the whole time of the arsenic administration no change took place in the number of red or white corpuscles nor in the amount of hæmoglobin, nor were any morphological changes observed in the cellular elements, although the blood was frequently examined both fresh and in films variously stained. On post-mortem examination no changes were found in any of the organs except the bone-marrow. (The cord and peripheral nerves were not examined microscopically however.) In all the bones the marrow was strikingly and quite distinctly of a deeper red colour than in the case of the control which had received no arsenic, and which was killed at the same time. The bone-marrow was fixed immediately in corrosive sublimate solution, hardened in alcohol, and then cut in paraffin. Numerous serial sections were made, and stained with hæmatoxylin and eosin, or with methyl-blue and eosin. The marrow from the control rabbit was treated in the same way.

OBSERVATION II. Duration 43 days.

Days 1—2. Control of blood examination. Red corpuscles 5,568,000 per cub. mm. Hæmoglobin 58 per cent.
 „ 3—43. 1/50—1/14 grain arsenious acid daily.

It died on the 43rd day with symptoms of paralysis. During all this time the corpuscles and hæmoglobin remained practically constant; the weight rose from 590 to 740 grms. and its health appeared perfectly good. The bone-marrow was much deeper in colour than in ordinary rabbits; it was preserved and examined as in Obs. I.

OBSERVATION III. Duration 82 days.

Days 1—3. Control of blood examination. Red corpuscles 5,360,000 to 5,600,000 per cub. mm. Hæmoglobin 65 per cent.
 „ 4—82. 1/50—1/12 grain arsenious acid daily.

All this time the rabbit remained in perfectly good health, and its weight increased from 520 to 820 grms. It was killed on the 83rd day, as was also one of the control rabbits, the weight of which had increased from 662 to 800 grms. On post-mortem examination both were found perfectly healthy in all respects, but the arsenic rabbit had bone-marrow of a much deeper colour than the other. The marrow from both was prepared and examined as before.

OBSERVATION IV. Duration 9 days.

This experiment was made on a young rabbit about 6 weeks old.

Days 1—2. Examination of blood.
 „ 3—9. 1/20 grain arsenious acid daily.

On the 9th day it died in complete paralysis, which came on suddenly. Its weight had increased from 415 to 430 grms., but no alteration whatever was observable in the blood. The bone-marrow of a much deeper colour than is usual.

The only changes which we observed, therefore, under the influence of arsenic were confined to the bone-marrow, the red-marrow being in every case increased in amount. We found no alteration in any of the viscera, nor in the corpuscles and hæmoglobin. The greatly increased formation of bone observed by Gies¹ in young rabbits under small doses of arsenic was not present in our animals, but his control animals in some cases showed a similar condition, and altogether it does not appear

¹ *Archiv f. expt. Path.* VIII. 1878.

to be a very constant effect. We are of opinion, however, that the new bone became somewhat more dense in the rabbits which received arsenic as compared with those which did not. The increase in weight and growth was practically at the same rate whether the rabbits got arsenic or not. We observed no fatty degeneration such as occurs in fatal poisoning with large doses of arsenic, nor was there any special increase of fatty or connective tissue anywhere.

Description of the Bone-marrow. The structure of normal bone-marrow from a young rabbit is shown in Figs. I. and III., under a low and higher power of the microscope respectively. It is made up of numerous large fat cells, very few capillaries, and ordinary nucleated marrow cells with a few red blood corpuscles free among them. An occasional large myelocyte is seen and a few eosinophil cells. Figs. II. and IV. show the appearance of the marrow in our rabbits which received arsenic. The difference is extremely striking, especially in the great increase in the number and size of the capillary vessels, which are distended with red blood corpuscles. There is also a much larger number of red corpuscles free among the marrow cells. The fat cells are much smaller and have to a large extent disappeared. The marrow cells also are greatly increased in number and are more closely packed together, this being allowed by the great diminution in the amount of fat. Under a higher power the fat cells which remain are seen to be small, and have an atrophied look. The large marrow cells in many instances contain bodies which seem to be red blood corpuscles, and several eosinophil cells are present in the field.

Stated shortly the marrow presents the following changes—greatly increased vascularity, a great diminution of fat, and a greatly increased number of marrow cells. The whole appearance denotes a general stimulation and increased function in the bone-marrow.

OBSERVATION V. Adult Rabbit. Duration 145 days.

Days 1—20. Control of blood examination. Red corpuscles 5,587,000 to 6,176,000 per cub. mm. Hæmoglobin 60—69 per cent.

„ 21—75. $1/25$ to $1/9$ grain arsenious acid daily.

„ 76—145. $1/9$ „ „

During this time its weight increased from 1950 to 1970 grms., it remained in good health, and the corpuscles and hæmoglobin kept within the original limits. There was no morphological change in the blood. The rabbit was killed at the same time as a control animal which had been kept under the same conditions. The organs of both were healthy.

In the arsenic rabbit the bone-marrow was somewhat more red than in the control, but the difference was not so marked as in the young animals. On microscopic examination, however, the same changes were seen as in the others, and are shown by comparing Figs. V. and VI. The changes are not so decided as in younger animals, but the increase in the blood supply and in the number of marrow cells and the decrease in the amount of fat are quite unmistakable. There is, in short, here also, evidence of very considerable stimulation of the marrow.

Observations on Dogs.

Five puppies were taken from the same litter of small terriers, and when five weeks old the arsenic was given to three of them daily by the mouth in milk.

OBSERVATION I. Duration 82 days. Red corpuscles 3,424,000 per cub. mm. Hæmoglobin 50 per cent.

Days 1—66. $1/50$ to $1/5$ grain arsenious acid daily.
 „ 66—82. $1/5$ „ „

It remained in good health and when killed all its organs were found to be healthy. The bone-marrow was slightly more red than in the control puppy. Its weight increased from 1195 to 2160 grms., and the corpuscles and hæmoglobin to 5,670,000 and 60 per cent. respectively. In the control the corpuscles and hæmoglobin had increased during this time from 4,048,000 and 45 per cent. to 6,090,000 and 60 per cent., and the weight from 945 to 2395 grms.

OBSERVATION II. Another of the dogs showed exactly the same conditions under arsenic and therefore we omit details, as the time and doses were almost exactly similar.

OBSERVATION III. Duration 112 days.

This dog got almost the same doses as in Obs. I. Its corpuscles and hæmoglobin increased from 3,080,000 and 45 per cent. to 5,660,000 and 60 per cent.; its weight from 835 to 1350 grms. In the control pup the corpuscles and hæmoglobin rose from 3,792,000 and 45 per cent. to 5,776,000 and 60 per cent.

Arsenic, therefore, in young healthy dogs cannot be said to have affected the red corpuscles and hæmoglobin, nor to have increased the body-weight, as compared with young dogs at the same age and growing rapidly. On microscopic examination the only change seen in the

bone-marrow of the arsenic dogs was a slight increase in the number and prominence of the capillary blood-vessels.

The changes in the bone-marrow of the dogs were much less marked than in the rabbits, and this may be due to the fact that the arsenic was given subcutaneously in the latter and by the mouth in the former. But it may depend on the animal rather than on the mode of administration. In this connection it is worthy of remark that in young rabbits no increase of the red corpuscles or hæmoglobin took place whether arsenic was given or not, but in young, growing dogs a great increase occurred both in the arsenic and non-arsenic animals. No other changes were visible in any of the viscera, and only very slightly in the bones.

CONCLUSIONS.

It is evident that in healthy animals arsenic does not increase the number of red or white corpuscles, nor the amount of hæmoglobin. This, however, is capable of being interpreted in two widely different ways: (1) The arsenic may stimulate the formation of red blood corpuscles, but there may occur simultaneously a corresponding increase in their breaking down, so as to keep the number present in the blood at a constant quantity. We found no evidence of increased breaking down so far as any increase of iron pigment could be detected in the liver, spleen, or other viscera. (2) *In health* there may be no increased formation of corpuscles under the action of arsenic. As before remarked it seems to be impossible by any method of treatment to increase the number of red corpuscles in health beyond their physiological maximum. A limit is apparently set, but by what physiological mechanism in the organism it is impossible to say in the present state of our knowledge. As iron, good food, tonics, and other means (except high altitude) all fail to increase the richness of the blood in corpuscles and hæmoglobin, it need not astonish us that arsenic also fails in health.

As regards its action as a hæmatinic in pernicious anæmia and other morbid conditions, our experiments point very conclusively to a stimulation of the bone-marrow. In these cases, however, although it may increase the number of blood corpuscles, it does not, so far as we can see, affect the real cause of the disease and therefore must be considered as a purely symptomatic method of treatment.

PLATE V.

1. Normal bone-marrow from upper end of femur of young rabbit, $\times 60$ diams. It shows numerous fat cells (the white spaces), marrow-cells, and two large blood-vessels in centre of field, but few elsewhere.

2. Bone-marrow from upper end of femur of young rabbit after administration of arsenic for 60 days, $\times 60$ diams. It shows the numerous blood-vessels, marrow-cells increased in number, very few fat cells and these distinctly atrophied. There is a large blood-vessel on left-hand side of figure.

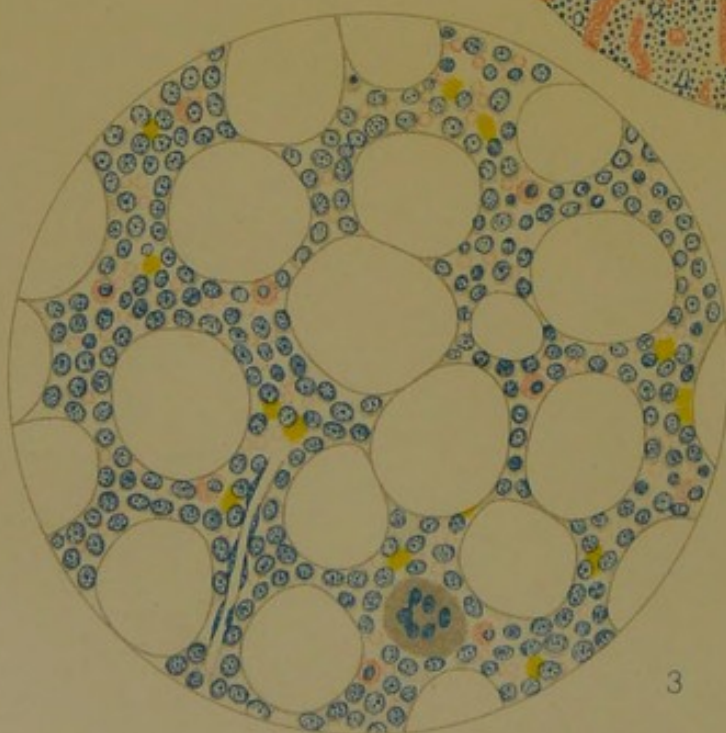
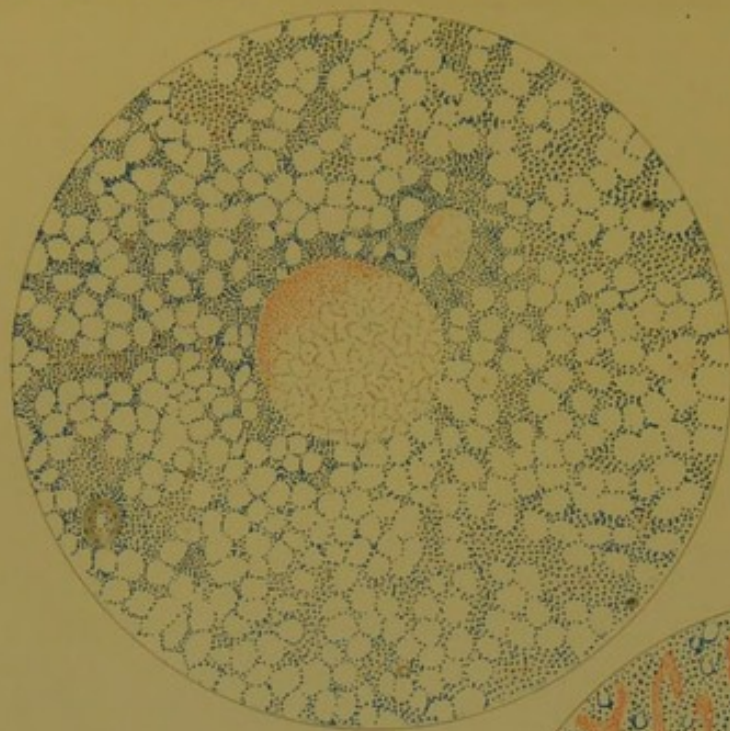
3. Same as Fig. 1 $\times 300$ diams. It shows numerous large fat cells, marrow-cells, a myelocyte, eosinophil cells, and some red blood-corpuscles.

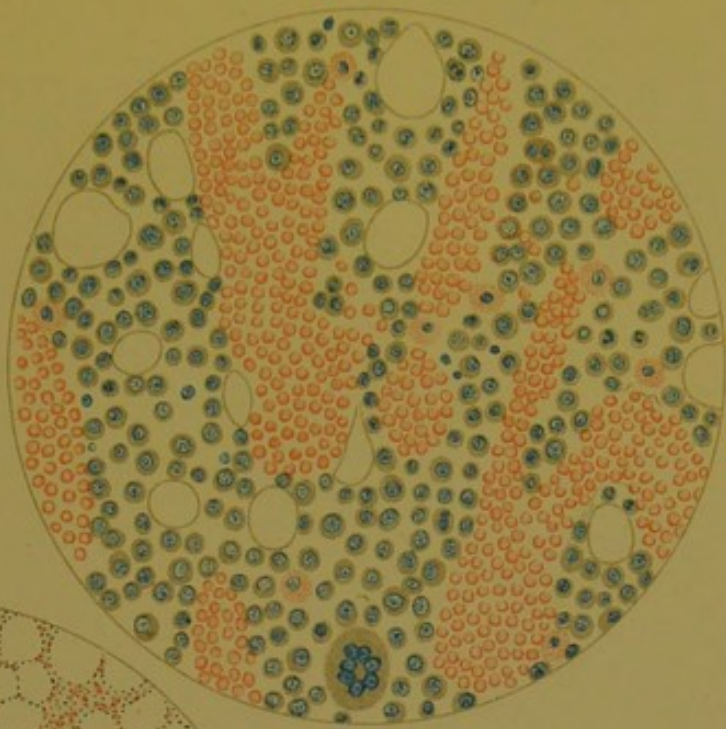
4. Same as Fig. 2 $\times 3000$ diams. It shows the blood-vessels greatly increased and filled with corpuscles, numerous marrow-cells, one myelocyte, fat cells few and atrophied, and eosinophil cells.

5. Normal bone-marrow from middle of femur of adult rabbit, $\times 60$ diams. It shows very numerous fat cells, marrow-cells, and a few small blood-vessels.

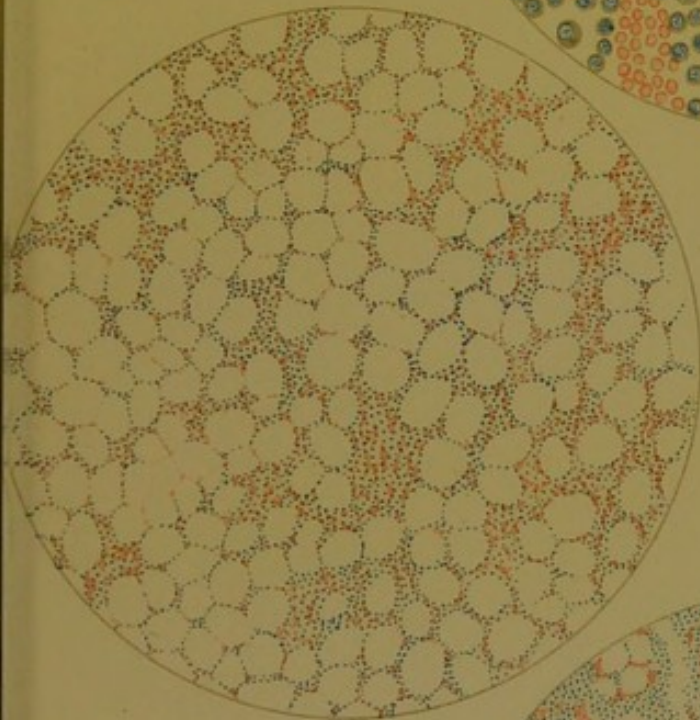
6. Bone-marrow from middle of femur of adult rabbit after administration of arsenic for 125 days. It shows increase in number and size of blood-vessels, decrease in number and size of fat cells, more numerous marrow-cells.



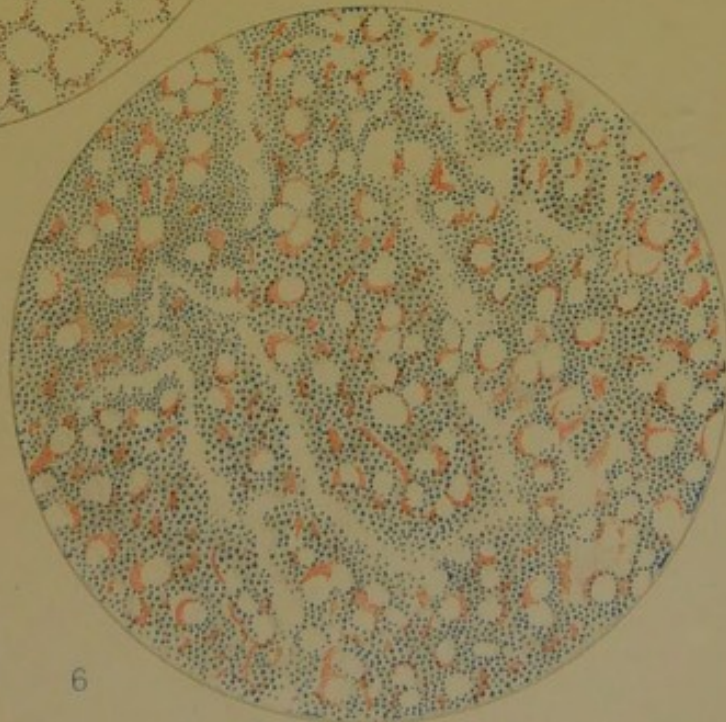




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