# LEUCOCYTIC CHANGES FOLLOWING THE INTRAVENOUS INJECTION OF PEPTONES.

by

D. G. COOPER, M.B., Ch.B.

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# LEUCOCYTIC CHANGES FOLLOWING THE INTRAVENOUS INJECTION OF PEPTONES.

During the winter 1925-26 a number of patients who were suffering from Rheumatoid Arthritis were treated in Ward 25 of the Royal Infirmary, Edinburgh, by intravenous injections of peptone.  The observations on which this thesis is based were made on these patients.  To Professor Murray-Lyon I am grateful for permission to make the observations and for much help while the work was in progress.

The number of cases is small.  Nevertheless, as the findings in the different series of observations agree so closely with each other and with related results obtained by other workers, they do provide data for a hypothesis.

The arrangement of this thesis will be:-

(1)  A general survey of the method.

(2)  A statement of cases with tables and graphs.

(3)  A general description of the results of the observations made.

(4)  A comparison of these results with those of other observers.

(5)  A discussion of the meaning of the observations.

(6)  A summary.

(7)  A list of references.

## GENERAL SURVEY OF THE METHOD.

Patients were given intravenous injections of peptone in increasing doses in accordance with the usual method for such treatment. After some of these injections examinations were made of the changes in the leucocyte picture and especially of the progressive changes in the numbers of neutrophil polymorphs when classified by Arneth's method.

The first two patients were only examined with a view to finding out whether a leucocytosis occurred, and to determining the nature of any increase in the white blood cells. It was found that a neutrophil polymorphonuclear leucocytosis did occur.

In subsequent cases this increase of polymorph leucocytes was analysed by means of Arneth's classification. In doing this I have followed the modification introduced by W.E. Cooke.

In each case a basal estimation was made immediately before the injection. (In some cases several estimations were made for a day or two before the injection. As they were found to agree in the main with the basal counts they have been omitted from the tables attached to the cases).

During the day of the injection from 3 - 7 observations were made at varying intervals. One was made on the following day. And in some cases further examinations/

examinations were made at intervals during the suc-
ceeding week.

Each observation consisted of two parts:-

(a) a total white cell count.

(b) a differential count combined with
an Arneth count.

(a) A Thoma Zeiss counting chamber was used for the
total count in the first few cases and a Bürker
for the rest.

(b) Blood smears were made after the blood had been
taken for the total count. These smears were
stained in various ways, some by Jenner's, some
by Leishman's, and some by the combined Jenner-
Giemsa method.
Combined differential and Arneth counts were
made of the stained smears. In most cases 250
or 300 cells were counted to make up the dif-
ferential count. Then more polymorph neutro-
phils were counted to bring the total polymorph
numbers up to a convenient figure for calculating
percentages. This figure varied from 150-300
in accordance with the numbers of the polymorphs.
The low figure of 150 was only considered suf-
ficient for slides taken during the period of
leucopenia; and then only when the total of the
leucocytes was below 4000 per ccm. As a rule
250 neutrophil polymorphs were counted.

Cooke's [1] modification of Arneth's classification
depends on the nature of the material linking or
separating the several nodes of the polymorph nucleus.
Some nuclei show no nodes at all.  In those nuclei
which do show lobulation, those segments are con-
sidered separate which are connected to the other
portions of the nucleus by chromatin threads alone.
If there is a distinct band of nuclear material with
the chromatin filament the lobe so connected is not
considered separate.

By this means polymorph neutrophils are divided
into five classes.



I          II          III          IV          V
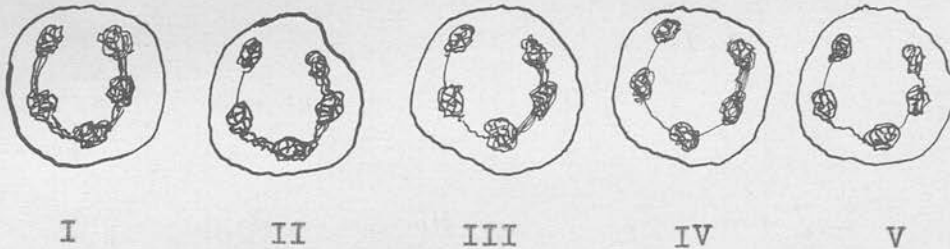
Class I     shows no separation into lobes, this
            includes those cells which show no nodes
            at all.  In these the nuclear matter looks
            like a ribbon and is often  S-shaped.
Class II    shows two segments.
Class III   shows three segments.
Class IV    shows four segments.
Class V     shows five or more segments.

The distinction between neutrophil myelocytes and
cells of class one is a very fine one.  When both
kinds/

kinds of cells appear in the peripheral circulation
one is often at a loss in distinguishing one from the
other.    As cells of Class I are the immediate suc-
cessors of myelocytes, and as myelocytes or an in-
crease in Class I cells both indicate bone marrow
activity, I have included myelocytes in Class I.
Only those cells have been classed as myelocytes which
showed acidophil cytoplasm, neutrophil granules, and
an approximately round nucleus.  Though I have class-
ified such cells as myelocytes, I have also added
them to Class I of the polymorphs.    Thus only a few
myelocytes are noted and though percentages and total
numbers are shown in the tables, these do not affect
the rest of the figures.

The actual numbers of leucocytes in Class V
are so insignificant that Classes IV and V have been
added together.

In practice it often happens that the different
segments of the nuclei are superimposed.    In many
cases the fine connecting strands can be seen, in
other cases it is not possible to be sure of their
presence or nature.    This circumstance tends to swell
the numbers of the cells with less complicated nuclei.
In all doubtful cases the cell has been placed in the
class with the more complicated nuclei.

## TABLES   AND   GRAPHS.

By means of these observations each case has provided a series of figures obtained at different stages of the peptone reaction.

These figures have been made into tables, and a graph has been constructed to illustrate each table.

To attain simplicity I have combined the figures for Classes I and II together, and Classes III, IV and V together in making the graphs. This does no violence to their meaning. Classes I and II are the juvenile cells, Class III consists of middle aged cells, Classes IV and V of aged cells. This question of age is not settled; it will be discussed later. An increase of Classes I and II is the same as Arneth's shift to the left and indicates bone marrow activity.

The small and large mononuclears have also been added together.

Peptone.    A 20% solution of Armour's ordinary peptone was used.  This consists of Primary Proteoses (approximately 0.4%), Secondary Proteoses (approximately 2.2%) and Peptone (approximately 0.3%).

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## ILLUSTRATIVE    CASES.

Case I.    Mc D., male, aged 57.   Suffering from
            Chronic Rheumatoid Arthritis.

This patient had had a series of injections which
commenced on 9.10.25.    Observations were made on him
on 13.11.25 after an injection of 1.75 ccs. of Armour's
Peptone.

9.30 a.m.    Armour's Peptone.  1.75 ccs. intravenously.

9.50 a.m.    W.B.C.  10,000

            Polymorphs.  68.5%       =   6850

            Small Mononuclears  17% =   1700

            Large Mononuclears  11% =   1100

            Eosinophils          2%  =   200

            Mast cells          1.5% =   150

10.30 a.m.   W.B.C.   9,200.

12.20 p.m.   W.B.C.   12,200.

 2.50 p.m.   W.B.C.   26,400.

4     p.m.   W.B.C.   28,000.

5.10 p.m.    W.B.C.   33,000

            Polymorphs    93.5%      =   31042

            Small Mononuclears  3%  =    996

            Large Mononuclears  3%  =    996

            Eosinophils          -        -

            Mast Cells          0.5 =.   166

As/

As only two differential counts and no Arneth counts
were made in this case, the figures have not been
tabulated and no graphs have been constructed.
But a graph of another kind has been made to show
the general reaction and the relation of the curve
showing leucocytosis to the curves of Temperature,
Pulse-rate, and Basal Metabolic rate.- Graph I.


Case II. Miss E.M., aged 28. This patient suffered
from Epileptiform Seizures. She was not
being treated with peptone alone. She was
given three injections while she was in
hospital.

| | |
|---|---|
| 28.10.25. | 0.75 ccs. |
| 9.11.25 | 1.2 ccs. |
| 11.11.25 | 0.75 ccs. |

Observations were made on one of these occasions.
No Arneth count was made. On another occasion blood
could not be obtained on account of a convulsion.
A record is shewn in Table I.


Case III. G.M., female, aged 24, suffered from
chronic Rheumatoid Arthritis. She re-
ceived ten injections. The amount of
the first injection was 0.25 ccs. and of the biggest
1.3 ccs. of Armour's peptone.
She/

She left hospital greatly improved.

Observations were made on the 14th and 18th of December 1925 and the 8th and 14th of January 1926. The results are shewn in Tables II, III, IV and V and the graphs of the same numbers.

In table II a considerable increase in mononuclears is shewn at the height of the increase. This will be discussed later.

Case IV.    J.B., male, age 56. Suffered from chronic Rheumatoid Arthritis. He was given injections of 0.25 ccs. of peptone on the 14th and 18th of December 1925, an injection of 0.75 ccs. on the 29th Dec. 1925, and one of 1.0 cc. on the 10th January 1926.

Records of the observations made on the 29th of December are shown in graph VI and table VI.

Case V.    Mrs S., age 45. Suffered from Chronic Rheumatoid Arthritis. This patient received an injection of 0.25 ccs. of peptone on the 1st of March 1926, and an injection of 0.5 ccs. on the 10th of March 1926. Observations were made on the 1st, 2nd, 5th, 8th, 9th, 10th, 11th and 16th, so that a fairly complete record has been obtained for sixteen days, during which time two injections were/

were given. Tables VII and VIII and graphs VII and
VIII show these results. Graph VIII and table VIII
are continuous with their forerunners.


Case VI.    J.S., female, age 18. Suffered from
            Lupus of the face. She was not treated
            with peptone but with injections of
Sanocrysin. Observations were made on the 2nd and
3rd and the 8th and 9th of February, after intravenous
injections of 1 gramme of Sanocrysin on each occasion.
The reactions were so similar to the reactions of
other patients after peptone that they have been
incorporated in this thesis.

        Tables IX and X and the graphs IX and X show
the results.

        The general reaction in this case was much less
severe than the reaction in cases after peptone.
She usually felt sick after an injection, and sometimes
suffered from a rise of temperature and an increase
in the pulse rate. But the degree of these was com-
paratively slight and she did not always need to go
to bed after an injection.


Case VII.   J.M., male, aged 21. This patient
            received a course of injections.
            Observations were made after an injection
            of/

of 0.25 ccs. of peptone on the 17th of February and
after 0.5 ccs. of peptone on the 11th of March.

The results are shown in tables **XI** and XII and
graphs XI and XII.

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I

J. McD.   13·11·25

Chart to show the relations of.   Temperature.
Pulse Rate.
Basal Metabolic Rate.
Leucocytosis

Leucocytes.

Peptone
1·75 cc

Temperature.  Pulse Rate.  Basal Metabolic Rate.

| Leucocytes | Temp | Pulse | BMR |
|---|---|---|---|
| 35000 | 104° | 180 | +60 |
| 30000 | 103° | 160 | +50 |
| 25000 | 102° | 140 | +40 |
| 20000 | 101° | 120 | +30 |
| 15000 | 100° | 100 | +20 |
| 10000 | 99° | 80 | +10 |
| 5000 | 98° | 60 | 0 |
| 0 | | | −10 |

Temperature.

Basal Metabolic Rate.

Pulse Rate.

Total Leucocytes.

Hours after Injection →   0   1   2   3   4   5   6   7   8
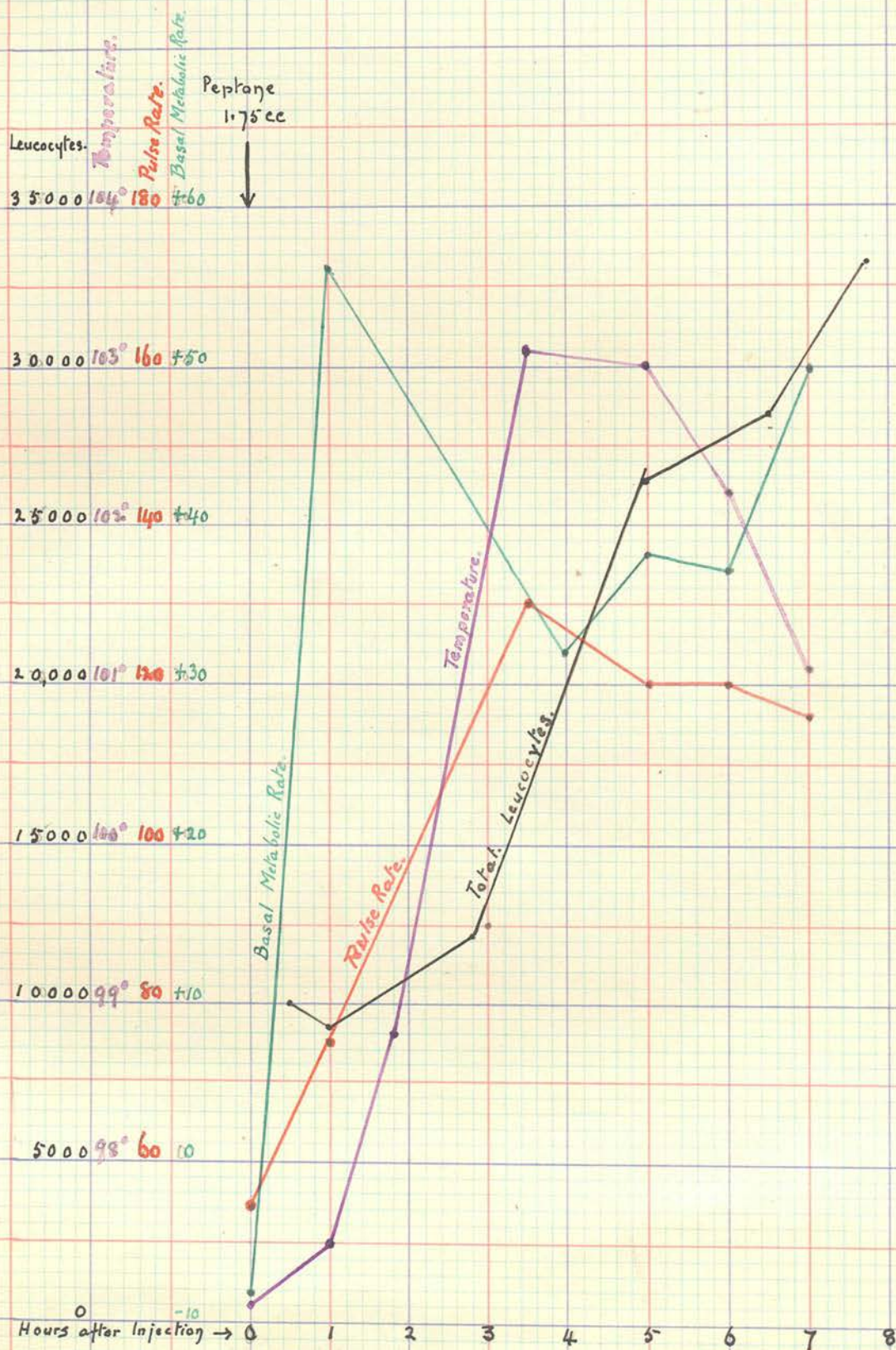
## TABLE I.

### ELLA MARTIN.  17.11.25 - Peptone 1 cc. at 9.30 a.m.

| Hours after injection. | $\frac{4}{5}$ | | $4\frac{1}{6}$ | | $3\frac{1}{5}$ | | $4\frac{5}{6}$ | | $6\frac{4}{6}$ | |
|---|---|---|---|---|---|---|---|---|---|---|
| | % | Total | % | Total | % | Total | % | Total | % | Total |
| Total Leucocytes. | | 7600 | | 8800 | | 16600 | | 27000 | | 26000 |
| Polymorphs. | 49.5 | 3762 | 75 | 6600 | 87.5 | 14525 | 93 | 25110 | 91.5 | 23790 |
| Small Mononuclears. | 34 | 2584 | 12.5 | 1100 | 8.5 | 1411 | 3 | 810 | 3.5 | 910 |
| Large Mononuclears. | 16 | 1216 | 12.5 | 1100 | 3.5 | 581 | 4 | 1080 | 4.5 | 1170 |
| Eosinophils. | 0.5 | 38 | - | - | 0.5 | 83 | - | - | - | |
| Mast. | - | - | | | | | | | 0.5 | 130 |

TABLE II.

GEORGINA MANSON.    14.12.25.

Peptone 1.0 cc. at 9.30 a.m.

| Time. | 9.30 a.m. | | 10.50 a.m. | | 1.55 p.m. | | 4.50 p.m. | | 5.55 p.m. | | 4.30 on 15 12/25 | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Hours after Injection. | 0 | | $1\frac{1}{3}$ | | $4\frac{1}{4}$ | | $7\frac{1}{3}$ | | $8\frac{1}{3}$ | | 31 | |
| Total Leucocytes | 8000 | | 5600 | | 15000 | | 16400 | | 14000 | | 4700 | |
| Total Polymorphs | 4200 | 52.5 | 4088 | 73 | 13425 | 89.5 | 10824 | 66. | 11410 | 81.5 | 3552 | 48. |
| I. | 294 | .7 | 492 | 12 | 2546 | 19 | 1790 | 16.5 | 2280 | 20 | 558 | 15.5 |
| II. | 987 | 23.5 | 1517 | 37 | 5494 | 41 | 5330 | 49 | 5529 | 48.5 | 1404 | 39 |
| III. | 1932 | 46 | 1558 | 38 | 3350 | 25 | 2870 | 26.5 | 3021 | 26.5 | 1314 | 36.5 |
| IV & V. | 987 | 23.5 | 533 | 13 | 2010 | 15 | 770 | 8 | 570. | 5. | 324 | 9. |
| Total Mononuclears | 3480 | 46 | 1400 | 25 | 1575 | 10.5 | 5226 | 32.5 | 2170 | 15.5 | 3700 | 50 |
| Eosinophil | 80 | 1 | 84 | 1.5 | – | – | 164 | 1 | 280 | 2. | 74 | 1 |
| Mast | – | – | – | – | – | – | 82 | 0.5 | 140 | 1 | 74 | 1 |

II

G. M. 14.12.25 — 15.12.25

Total Leucocytes.
" Polymorphs.
" Arneth Classes I & II
" " " III, IV, & V
" Mononuclears.
Broken line indicates a long interval.

For an explanation of the lines
made by question marks. see.
the discussion on mononuclears.

Peptone.
Injection
1.0 ccs.

Hours after
Injection → 0   1   2   3   4   5   6   7   8   9 — — — 24 — 31

TABLE III.

GEORGINA MANSON.    $\frac{18}{19}$. 12. 25.

Peptone. 1-2 cc. at 9.30 a.m.

| Time | 9.30 a.m. | | 11.10 a.m. | | 3.10 p.m. | | 4.20 p.m. | | 7 p.m. | | 10.45 a.m. $19\frac{12}{25}$ | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Hours after injection. | 0 hours | | $1\frac{2}{3}$ | | $5\frac{2}{3}$ | | $6\frac{5}{6}$ | | $9\frac{1}{2}$ | | $24\frac{1}{4}$ | |
| Total Leucocytes | | 6200 | | 4000 | | 17800 | | 16800 | | 17500 | | 11,000 |
| Total Polymorphs | 72 | 4464 | 59.6 | 2384 | 94.4 | 16800 | 94 | 15794 | No differential | | 81 | 8910 |
| I | 7.6 | 342 | 35.5 | 845 | 31 | 5200 | 34 | 5392 | Count. | | 23 | 2050 |
| II | 31.2 | 1390 | 38.5 | 920 | 42 | 7030 | 44 | 6952 | - | | 43.5 | 3860 |
| III | 46. | 2050 | 22.5 | 538 | 25 | 4200 | 19 | 3000 | | | 27.5 | 2450 |
| IV & V | 15.2 | 654 | 3.5 | 84. | 2 | 336 | 3 | 474 | | | 6 | 538 |
| Total Mononuclears | 27 | 1924 | 39.6 | 1484 | 5.6 | 1000 | 5 | 840 | | | 18 | 1930 |
| Eosinophil | 1 | 62 | 0.4 | 16 | - | - | 1 | 170 | | | 1 | 110 |
| Mast. | - | | - | | - | | | | | | | |

III

G.M. 18.12.25 — 19.12.25.
Total Leucocytes.
    „ Polymorphs.
    „ Arneth Classes. I & II
    „ „ „ III, IV & V
    „ Mononuclears.
Broken line indicates a long interval.
No differential count was done at the
9th hour. The figures here are computed
and indicated by question marks.

Peptone.
Injection
1·2 ccs.

20000
19000
18000
17000
16000
15000
14000
13000
12000
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000

Hours after
Injection → 0   1   2   3   4   5   6   7   8   9 — — 24

TABLE IV.

**GEORGINA MANSON.  8.1.26 and 9.1.26.**

Peptone 1.1 cc. at 10 a.m. 8.1.26.

| Date | 8.1.26 | | 8.1.26 | | 8.1.26 | | 8.1.26 | | 8.1.26 | | 8.1.26 | | 8.1.26 | | 9.1.26 | |
| Time and Hours after injection. | 9.50 a.m. 0 | | 10.35 a.m. $\frac{1}{2}$ | | 11.10 a.m. 1$\frac{1}{6}$ | | 12.30 p.m. 2$\frac{1}{2}$ | | 4 p.m. 6 | | 5 p.m. 7 | | 8 p.m. 10 | | 11 a.m. 25 | |
| | Totals | % | Total | % | Total | % | Total | % | Total | % | Total | % | Total | % | Total | % |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Total Leucocytes | 8400 | | 6200 | | 5600 | | 7800 | | 14600 | | 14900 | | 18000 | | 10,000 | |
| Total Polymorphs | 5964 | 71 | 4005 | 64.6 | 4122 | 73.6 | 6591 | 84.5 | 13432 | 92 | 13320 | 90 | 16416 | 91.2 | 7140 | 71.4 |
| I | 438 | 7.3 | 480 | 12 | 574 | 14 | 1782 | 27 | 3296 | 24.6 | 3458 | 26 | 5248 | 32 | 710 | 10 |
| II | 1260 | 21 | 1200 | 30 | 1681 | 41 | 2805 | 42.5 | 5816 | 43.4 | 6251 | 47 | 7216 | 44 | 3124 | 44 |
| III | 2760 | 46 | 1680 | 42 | 1537 | 37.5 | 1914 | 29 | 3538 | 26.4 | 3059 | 23 | 3149 | 19.2 | 2485 | 35 |
| IV & V | 1536 | 25.6 | 640 | 16 | 308 | 7.5 | 99 | 1.5 | 750 | 5.6 | 532 | 4 | 787 | 4.8 | 781 | 11 |
| Mononuclears | 2268 | 27 | 2071 | 33.4 | 1456 | 26 | 1209 | 15.5 | 1168 | 8 | 1480 | 10 | 1584 | 8.8 | 2860 | 28.6 |
| Eosinophils | 126 | 1.5 | 124 | 2.0 | 22 | 0.4 | - | - | - | - | - | - | - | - | - | - |
| Mast Cells | 42 | 0.5 | - | - | - | - | - | - | - | - | - | - | - | - | - | - |

IV

G.M  8.1.26 — 9.1.26.
The coloured lines indicate
the same classes as in the
preceeding diagrams.

Peptone.
Injection
1·1 ccs.

Total Leucocytes.

Total Polymorphs.

Arneth Classes I & II

Arneth Classes III, IV & V

Mononuclears.

Hours after
Injection →   0   1   2   3   4   5   6   7   8   9 — 10 — 24 hr. — 24
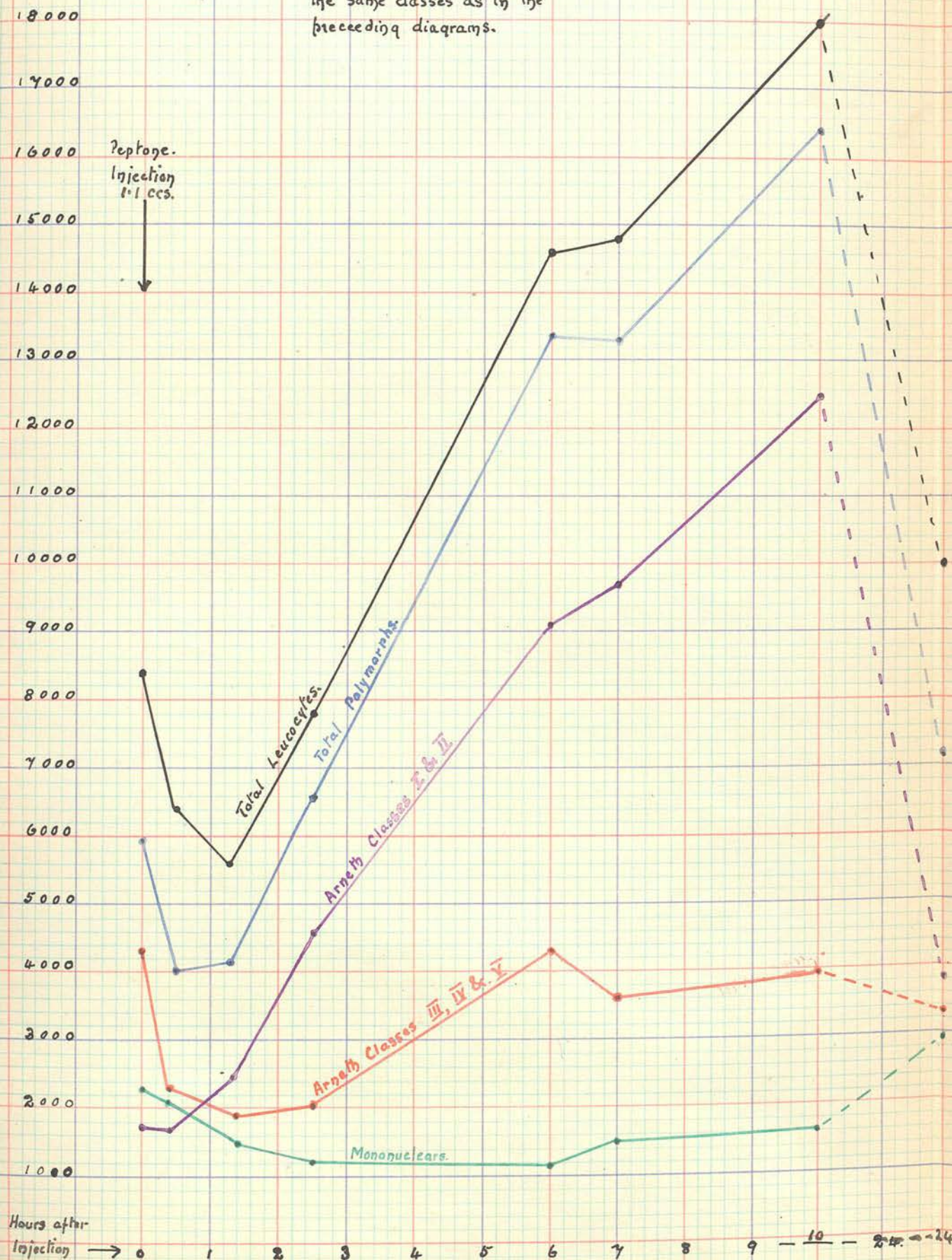
## TABLE V.

### GEORGINA MANSON. 14.1.26.

Peptone 1 cc. at 9.30

| Date | 7.1.26 | | 14.1.26 | | 14.1.26 | | 14.1.26 | | 15.1.26 | |
|---|---|---|---|---|---|---|---|---|---|---|
| Time | 10 a.m. | | 11.40 | | 2.15 | | 3.45 | | 11 a.m. | |
| Hours after Injection. | 0 * | | 2 10/60 | | 4 45/60 | | 6 1/4 | | 25 1/2 | |
| | % | Totals | Totals | % | Totals | % | Totals | % | % | Totals |
| Total Leucocytes | | 8400 | 12000 | | 11000 | | 12000 | | | 9600 |
| Total Polymorphs | 62. | 5208 | 8520 | 71 | 9856 | 89.6 | 10320 | 86 | 60 | 5760 |
| Arneth I. | 4.4 | 230 | 4590 | 54 | 5187 | 52.4 | 5922 | 57.5 | 23.3 | 1351 |
| Arneth II. | 25.2 | 1310 | 2924 | 34.4 | 2732 | 27.6 | 2987 | 29 | 46 | 2668 |
| Arneth III. | 44.4 | 2300 | 918 | 10.8 | 1306 | 13.2 | 1081 | 10.5 | 27.3 | 1583 |
| " IV & V. | 26 | 1360 | 68 | 0.8 | 673 | 6.9 | 309 | 3.0 | 3.3 | 191 |
| Mononucleears | 36.6 | 3074 | 3264 | 27.2 | 1078 | 9.8 | 1620 | 13.5 | 34.4 | 3303 |
| Eosinophils | 1.1 | 92 | 96 | 0.8 | – | – | – | – | 2.4 | 230 |
| Mast Cells | 0.3 | 26 | 120 | 1.0 | 66 | 0.6 | 60 | 0.5 | 3.2 | 307 |

\* In this case several normal counts had been done. As it happened no basal count was made on the day of injection so a previous day's normal count has been used.

V

G.M.   14.1.26  —  15.1.26.
The various colours have the
same meanings as in other
diagrams.

Peptone
Injection
1·1 cc

20000
19000
18000
17000
16000
15000
14000
13000
12000
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000

Total Leucocytes.

Total Polymorphs

Arneth classes I & II

Mononuclears

Arneth classes III, IV, V & V
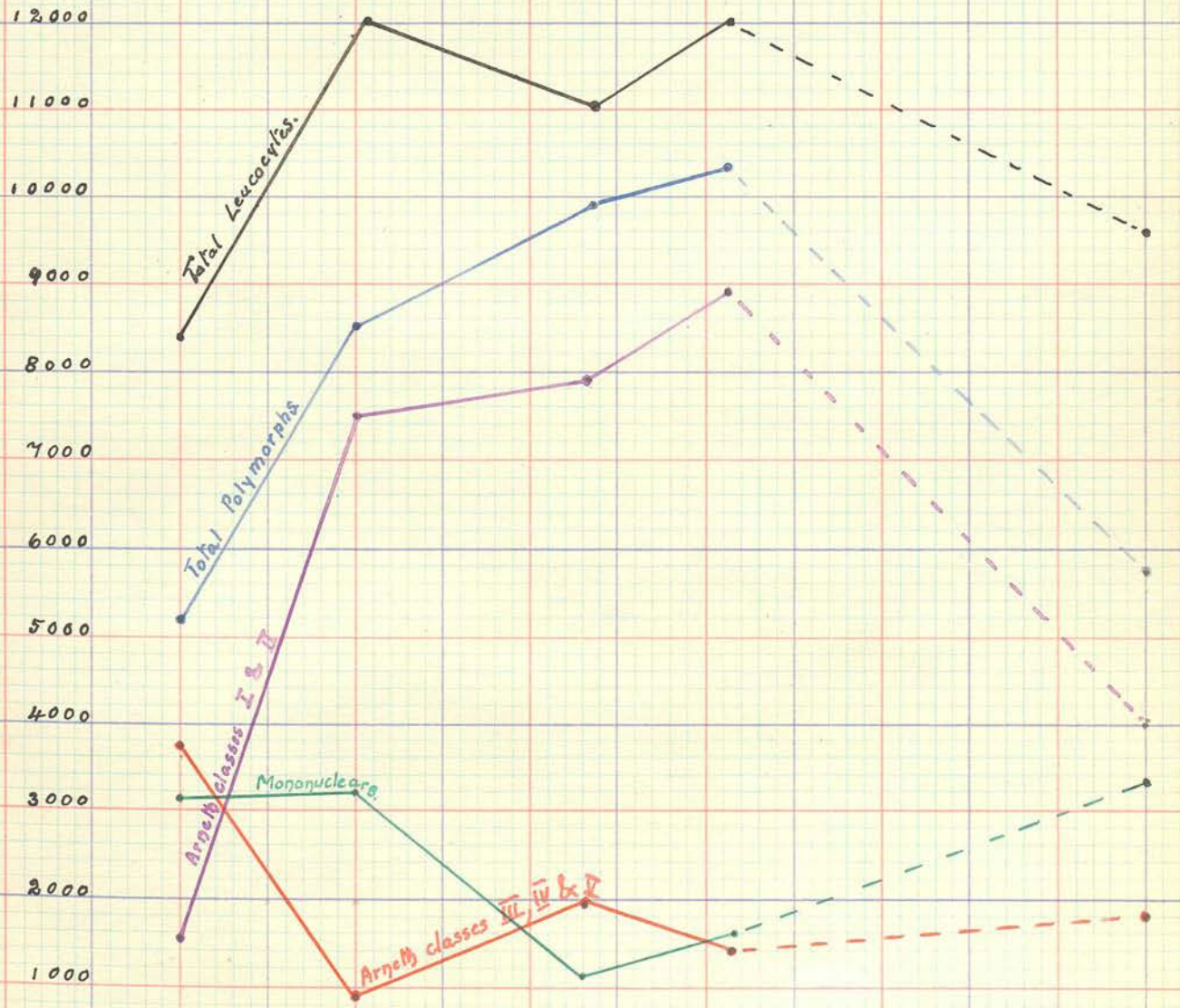
Hours after
Injection →   0   1   2   3   4   5   6   7   8   9  — — — 24.

TABLE VI.

**JAMES BROCKIE.** 29.12.25.

Peptone at 9.30 a.m.
1.0 cc.

| Time and Hours after injection. | 10 a.m. ½ hour. | | 11.10 a.m. 1⅔ hours | | 12.10 p.m. 2⅔ hours | | 2.50 p.m. 5⅓ hours | | 4.40 p.m. 7⅙ hours | | 2.30 p.m. on 30 12/25 29 hours. | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | % | | % | | % | | % | | % | | % | |
| Total Leucocytes | | 9800 | | 9200 | | 12000 | | 14200 | | 12800 | | 8600 |
| Total Polymorphs | 78 | 7644 | 89.5 | 8234 | 90.8 | 10896 | 84.8 | 12041 | 74 | 9472 | 56. | 4816 |
| I | 6.5 | 497 | 19 | 1560 | 23.2 | 2505 | 22.8 | 2730 | 22 | 2080 | 6.5 | 312 |
| II | 21.5 | 1641 | 36.5 | 3000 | 44 | 4800 | 44.4 | 5328 | 47.4 | 4479 | 32.5 | 1560 |
| III | 53.5 | 4080 | 34 | 2780 | 25.6 | 2800 | 25.2 | 3024 | 20 | 1890 | 41.5 | 1992 |
| IV & V. | 18.5 | 1414 | 10.5 | 864 | 7.2 | 787 | 7.6 | 912 | 10.6 | 1010 | 19.5 | 936 |
| Monomuclears | 21.2 | 2078 | 9. | 828 | 9.2 | 1104 | 14.4 | 2044 | 26 | 3328 | 40.4 | 3474 |
| Eosinophils | 0.8 | 78 | 1.5 | 138 | - | - | 0.8 | 113 | - | - | 3.6 | 310 |
| Mast | | | | | | | | | | | | |

VI

J.B.    29·12·25 — 30·12·25.

Broken lines. indicate a long interval.

Peptone. Injection. 1·0 ccs.

Total Leucocytes.

Total Polymorphs

Arneth Classes I & II

Arneth classes. III, IV & V

Mononuclears

20000
19000
18000
17000
16000
15000
14000
13000
12000
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000

Hours after Injection → 0   1   2   3   4   5   6   7   8   9 — — — 29
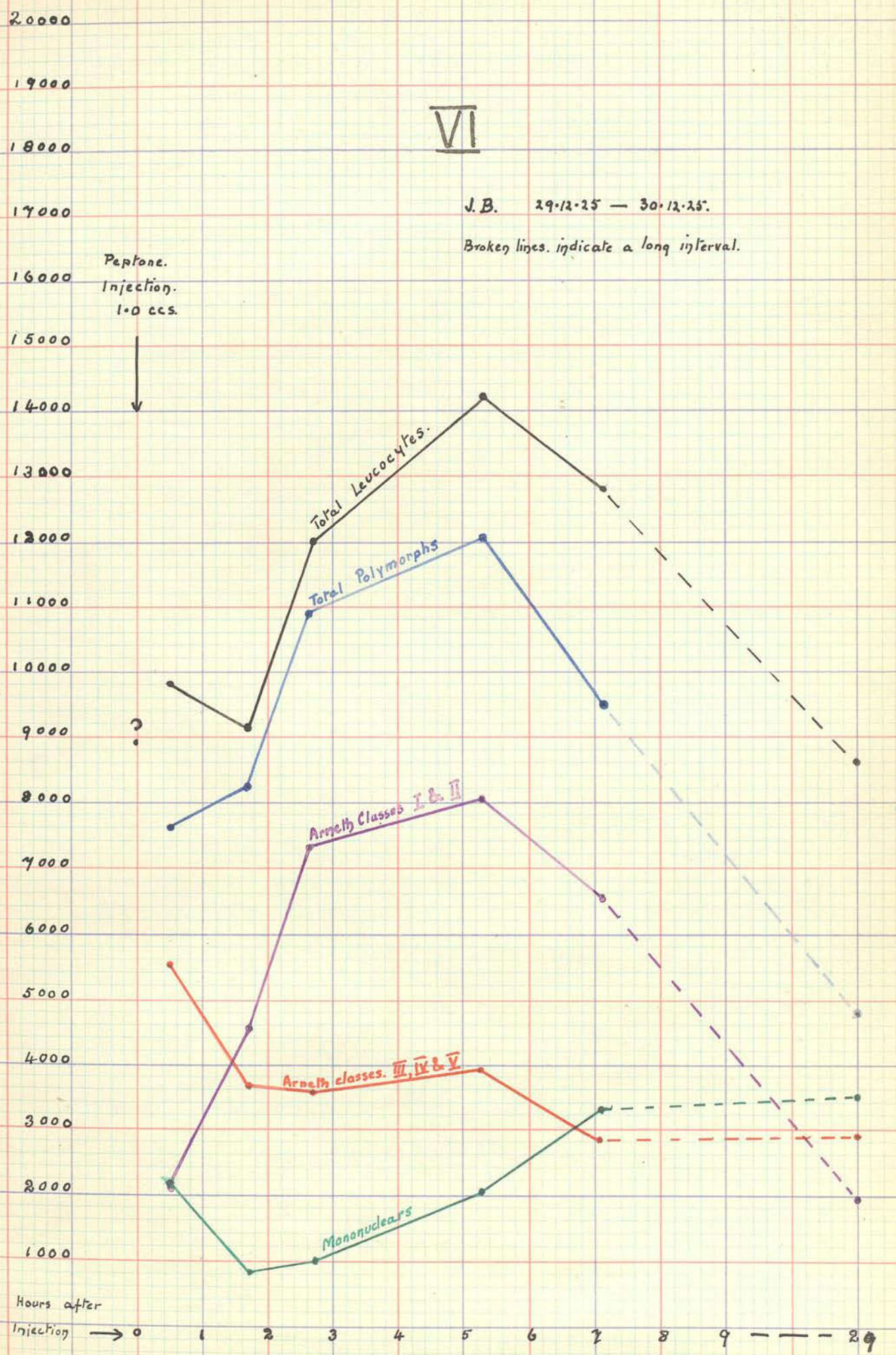
TABLE VII.

MRS STEWART.   1.3.26

Armour's Peptone   0.25 at 11 a.m.

| Date | 1.3.26 |  | 1.3.26 |  | 1.3.26 |  | 1.3.26 |  | 1.3.26 |  | 2.3.26 |  | 3.3.26 |  | 5.3.26 |  | 8.3.26 |  | 9.3.26 |  |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Time | 10.50 a.m. |  | 11.50 a.m. |  | 12.50 |  | 3.20 p.m. |  | 7.20 p.m. |  | 11 a.m. |  | 11 a.m. |  | 11 a.m. |  | 11 a.m. |  | 11 a.m. |  |
| Hours after injection. | 0 |  | $\frac{5}{6}$ |  | $1\frac{5}{6}$ |  | $4\frac{1}{3}$ |  | $8\frac{1}{3}$ |  | 24 |  | 48 |  | 96 |  | 168 |  | 192 |  |
|  | No. | % | No. | % | No. | % | No. | % | No. | % | No. | % | No. | % | No. | % | No. | % | No. | % |
| Total Leuco-cytes | 4800 |  | 2000 |  | 3500 |  | 6360 |  | 14500 |  | 10000 |  | 6840 |  | 4600 |  | 4500 |  | 6400 |  |
| Poly-morphs | 2807 | 56.4 | 1030 | 51.5 | 2905 | 83 | 6068 | 94.8 | 13804 | 95.2 | 9250 | 92.5 | 4461 | 65.6 | 3460 | 75.2 | 2277 | 50.6 | 3174 | 49.6 |
| Arneth I | 616 | 22 | 337 | 33.7 | 1726 | 59.5 | 3599 | 59. | 9219 | 66.8 | 5428 | 59. | 1957 | 43.5 | 840 | 24. | 679 | 29.5 | 877 | 27.4 |
| II | 784 | 28 | 426 | 42.6 | 793 | 27 | 1830 | 30 | 3036 | 22 | 2714 | 29.5 | 1610 | 36 | 1190 | 34 | 851 | 37 | 1450 | 45.4 |
| III | 1100 | 39.3 | 200 | 20. | 348 | 12 | 549 | 9 | 1270 | 9.2 | 966 | 10.5 | 698 | 15.5 | 966 | 27.6 | 575 | 25. | 787 | 24.6 |
| IV & V | 296 | 10.6 | 38 | 3.7 | 43 | 1.5 | 122 | 2 | 276 | 2.0 | 92 | 1.0 | 135 | 3.0 | 504 | 14.4 | 195 | 8.5 | 83 | 2.6 |
| Mono-nuclear | 1977 | 41.2 | 930 | 46.5 | 560 | 16. | 281 | 4.4 | 696 | 4.8 | 750 | 7.5 | 2203 | 32.4 | 1104 | 24. | 1926 | 42.8 | 3150 | 49.2 |
| Eosino-phils | 96 | 2.0 | 40 | 2.0 | 35 | 1. | 51 | 0.8 | - | - | - | - | 136 | 2. | 18 | 0.4 | 297 | 6.6 | 76 | 1.2 |
| Mast Cells | 20 | 0.4 | - | - | - | - | - | - | - | - | - | - | - | - | 18 | 0.4 | - | - | - | - |
| Myelo-cytes | - | - | 12 | 0.6 | 122 | 3.5 | 205 | 3.2 | 232 | 1.6 | - | - | - | - | - | - | - | - | - | - |

VII

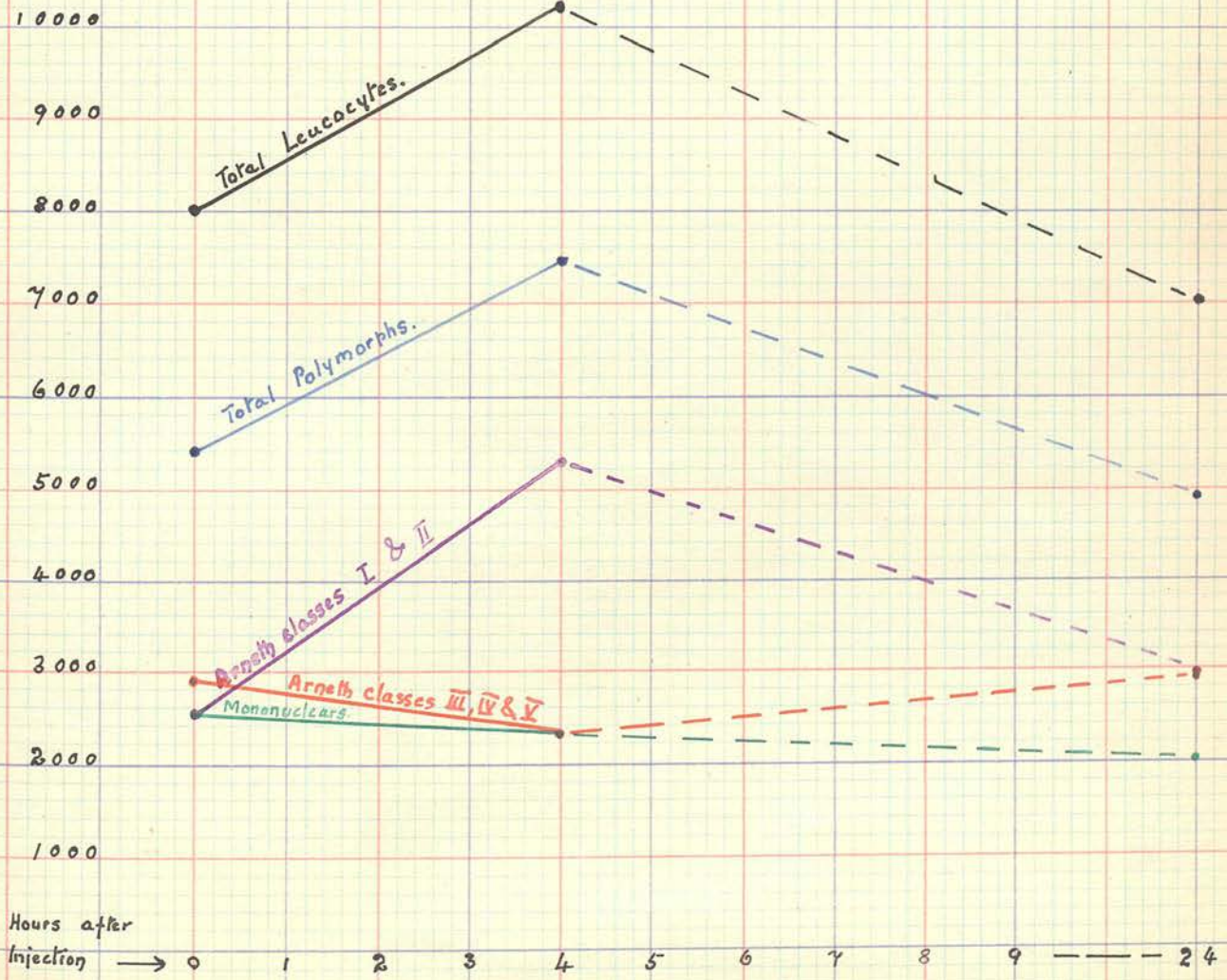Mrs S.    1.3.26 — 9.3.26.
Broken lines indicate long intervals.

Peptone.
Injection
0.25 ccs.

20000
19000
18000
17000
16000
15000
14000
13000
12000
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000

Total Leucocytes.
Total Polymorphs.
Arneth Classes I & II.
Arneth Classes III, IV & V.
Total Mononuclears.

Hours after
Injection →    0    1    2    3    4    5    6    7    8    9    24    48    96    168    192
                                                        1 day.   2 days.   4 days.   7 days.   8 days.
                                                        2.3.26   3.3.26   5.3.26   8.3.26   9.3.26
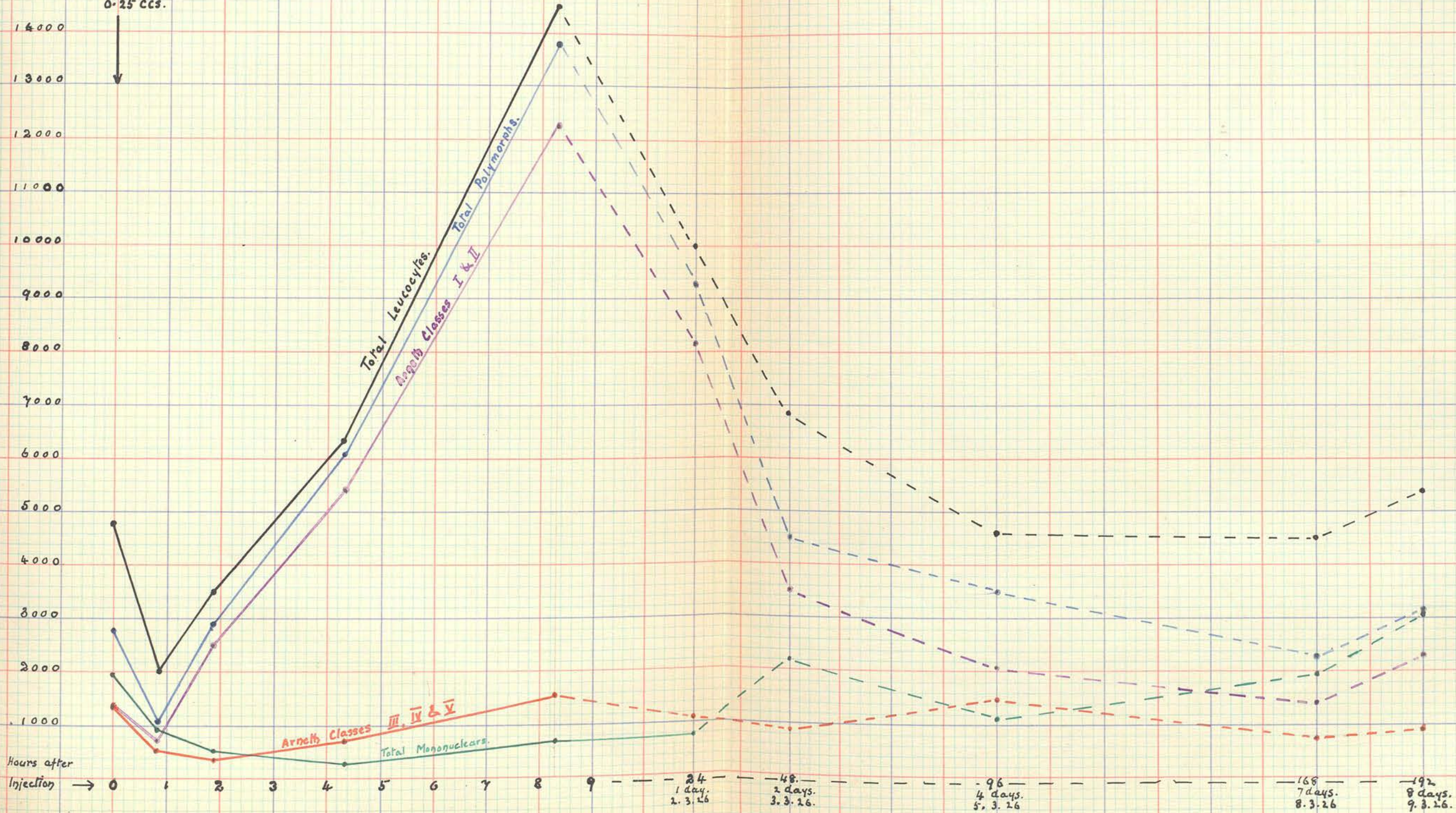
TABLE VIII.

**MRS STEWART.**  10.3.26 — 16.3.26.

Peptone  0.5 cc. on 10.3.26 at 10.30.

| | 10.3.26 10.25 a.m. (0) | | 10.3.26 11.30 (1) | | 10.3.26 12.30 (2) | | 10.3.26 3 p.m. (4½) | | 10.3.26 6 p.m. (7½) | | 11.3.26 10.30 (24) | | 16.3.26 10.30 (134) | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | % | Totals | % | Totals | % | Totals | % | Totals | % | Totals | % | Totals | % | Totals |
| Total Leucocytes | | 5700 | | 2900 | | 5900 | | 9100 | | 15600 | | 5700 | | 4100 |
| Polymorphs | 54 | 3078 | 62.4 | 1810 | 82. | 4838 | 92 | 8370 | 95.2 | 14851 | 64 | 3648 | 47 | 1927 |
| Arneth I. | 24.5 | 760 | 50.5 | 909 | 58.1 | 2789 | 60.4 | 5074 | 54. | 8019 | 25 | 900 | 26 | 494 |
| Arneth II. | 36.5 | 1131 | 35 | 630 | 32.5 | 1560 | 27.6 | 2318 | 32 | 4752 | 41 | 1476 | 37 | 702 |
| Arneth III. | 33 | 1023 | 14 | 252 | 7.5 | 360 | 10.8 | 807 | 11.6 | 1722 | 31 | 1116 | 31 | 589 |
| " IV & V. | 6.0 | 186 | 0.5 | 9 | 1.9 | 91 | 1.2 | 101 | 2.4 | 357 | 3 | 108 | 6 | 114 |
| Mononuclears | 42.8 | 2439 | 33.6 | 974 | 18 | 1062 | 8.0 | 730 | 4.8 | 749 | 32.8 | 1870 | 47.5 | 1949 |
| Eosinophils | 3.2 | 183 | 4.0 | 116 | | | | | | | 3.2 | 182 | | |
| Mast Cells. | — | — | | | | | | | | | | | | |
| Myelocytes which are included in P.M. | | — | | — | 1 | 59 | 0.4 | 36 | 1.0 | 156 | | — | | — |

VIII

Mrs S.    10.3.26  ——  16.3.26.
The broken lines indicate long intervals.

Peptone.
Injection
0.5 ccs.

Total Polymorphs.

Arneth I & II.

Arneth III, IV & V.

Mononuclears.

Hours after
Injection →    0    1    2    3    4    5    6    7    8    9    24    144
                                                             1 day    6 days.
                                                          11.3.26.   16.3.26.
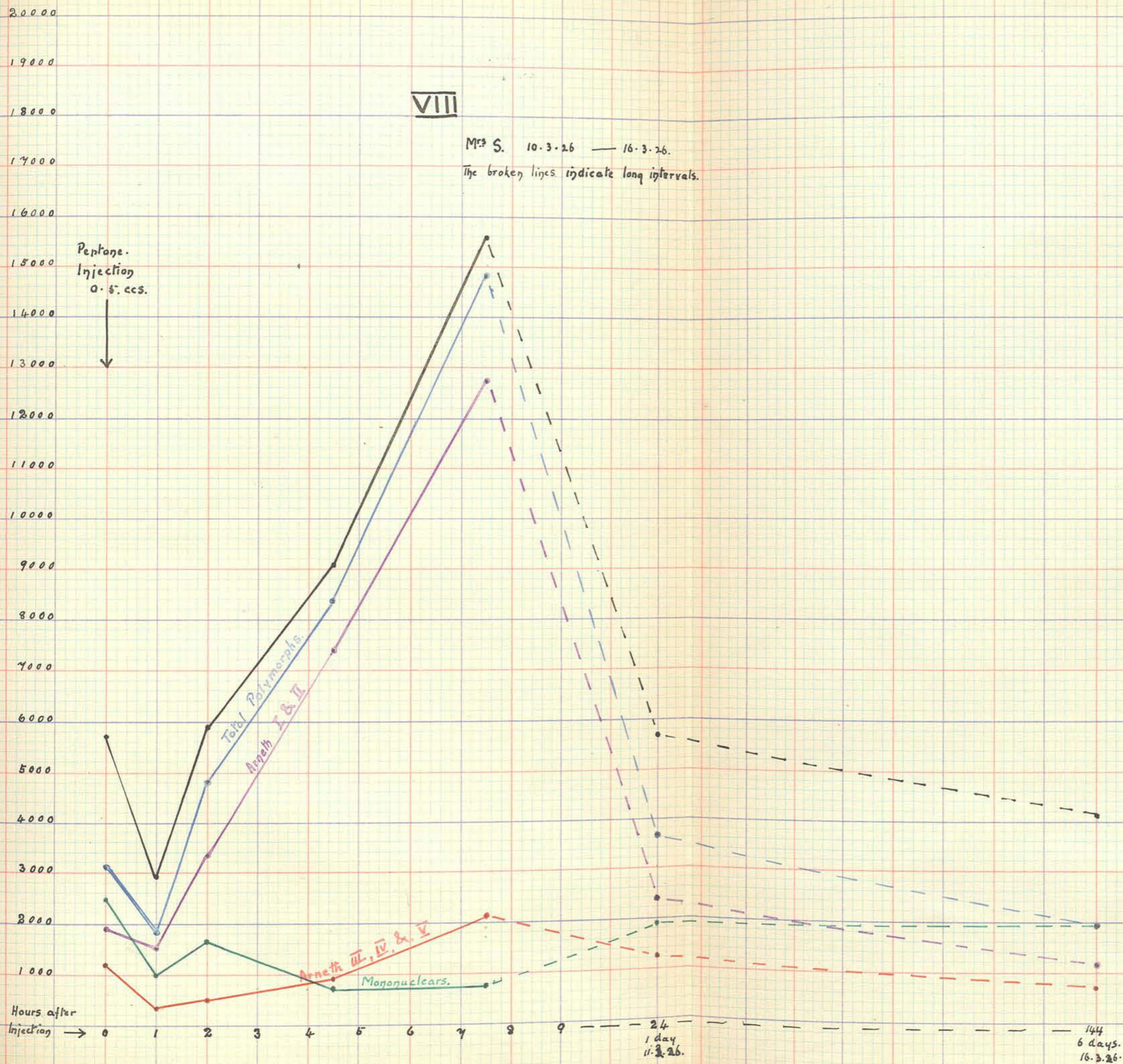
## TABLE IX.

## JESSIE STENHOUSE. 2.2.26.

Sanocrysin gramme 1.0 at 11.40 a.m.

| | 2.2.26 | | 2.2.26 | | 2.2.26 | | 2.2.26 | | 3.2.26 | |
|---|---|---|---|---|---|---|---|---|---|---|
| Date | 11 a.m. | | 1.10 p.m. | | 3.15 p.m. | | 8 p.m. | | 11 a.m. | |
| Time | | | | | | | | | | |
| Hours after Injection. | 0 | | 1½ | | 3½ | | 7½ | | 23 | |
| | % | Totals | % | Totals | % | Totals | % | Totals | % | Totals. |
| Total Leucocytes | | 6400 | | 8200 | | 10600 | | 6000 | | 5900 |
| Total Polymorphs | 70.8 | 4531 | 73.2 | 6005 | 75.2 | 7961 | 79.6 | 4776 | 77.2 | 4477 |
| Arneth I | 18. | 810 | 28.5 | 1710 | 24.8 | 1984 | 16.0 | 768 | 23.5 | 1034 |
| " II | 32.5 | 1462 | 34.5 | 2070 | 40.4 | 3232 | 28.4 | 1363 | 31.5 | 1386 |
| " III | 36.5 | 1642 | 29. | 1740 | 25.2 | 2016 | 40.4 | 1940 | 37.3 | 1650 |
| " IV & V | 13.0 | 584 | 8.0 | 480 | 9.6 | 768 | 15.2 | 729 | 7.5 | 330 |
| Mononuclears | 27.6 | 1765 | 25.2 | 2065 | 23.6 | 2502 | 20.2 | 1152 | 20.4 | 1183 |
| Eosinophils | 0.8 | 51 | 0.4 | 32 | 0.8 | 85 | 0.4 | 24 | 1.2 | 70 |
| Mast Cells | 0.8 | 51 | 1.2 | 98 | 0.4 | 42 | 0.8 | 48 | 1.2 | 70 |

IX.

J.S.  2.2.26 — 3.2.26.
Broken lines indicate long intervals.

Sanocrysin
1 Gramme.

Total Leucocytes.

Total Polymorphs

Arneth classes I & II

Arneth classes III, IV & V

Mononuclears
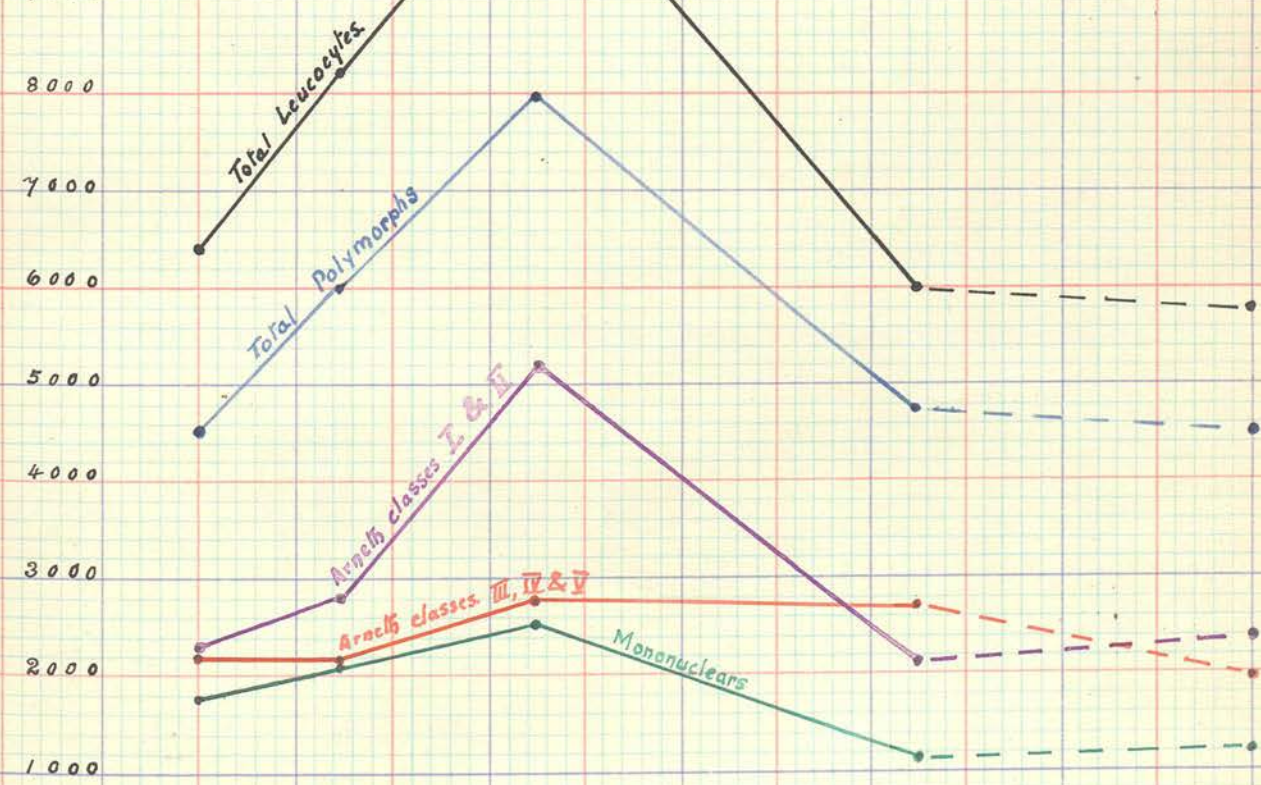
Hours after Injection → 0 1 2 3 4 5 6 7 8 9 — — — 24.

TABLE X.    JESSIE STENHOUSE.    8.2.26.

Sanocrysin 1 gramme at 11 a.m.

| | 8.2.26. | | 8.2.26. | | 9.2.26. | |
| Date. | 10.35 | | 3 p.m. | | 11 a.m. | |
| Time. | | | | | | |
| Hours after injection | 0 | | 4 | | 24. | |
| | % | Total | % | Total | % | Total. |
| Total Leucocytes | | 8000 | | 10200 | | 7000 |
| Total Polymorphs | 67.5 | 5400 | 74.9 | 7630 | 70 | 4900 |
| Arneth I | 12. | 648 | 26.5 | 2014 | 20.8 | 1020 |
| " II | 34 | 1836 | 43. | 3268 | 39.6 | 1940 |
| " III | 41.3 | 2230 | 26 | 1976 | 31.2 | 1528 |
| " IV & V | 12.6 | 680 | 4.5 | 342 | 8.4 | 412 |
| Mononuclears | 31.5 | 2520 | 22.8 | 2328 | 29.8 | 2016 |
| Eosinophils | 1.0 | 80 | 2. | 202 | - | - |
| Mast Cells | - | - | | | | |
| Myelocytes | | | 0.4 | 40 | 0.4 | 28 |

X

J.S.   8.2.26 — 9.2.26.
Broken lines indicate long intervals.

20000
19000
18000
17000
16000
15000
14000
13000   Sanocrysin
         1 Gramme.
12000
11000
10000
9000
8000    Total Leucocytes.
7000
6000    Total Polymorphs.
5000
        Arneth classes I & II
4000
3000    Arneth classes III, IV & V
        Mononuclears.
2000
1000

Hours after
Injection  ⟶  0   1   2   3   4   5   6   7   8   9  — — — 24

TABLE XI.

**J. MACDONALD.**   17.2.26.

Peptone   0.25 cc. at 12.30 p.m.

| Date. | 17.2.26 | | 17.2.26 | | 17.2.26 | | 17.2.26 | | 17.2.26 | | 17.2.26 | | 18.2.26 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Time. | 10 a.m. | | 1 p.m. | | 1.45 p.m. | | 3.10 p.m. | | 4 p.m. | | 7.5 p.m. | | 11 a.m. | |
| Hours after Injection. | 0 | | $\frac{1}{2}$ | | $1\frac{1}{4}$ | | $2\frac{4}{6}$ | | $3\frac{1}{2}$ | | $6\frac{3}{4}$ | | 23 | |
|  | Total | % | Total | % | % | Total | % | Total | % | Total | % | Total | % | Total |
| Total Leucocytes | 8400 |  | 10,000 |  |  | 11,000 |  | 11600 |  | 12000 |  | 19800 |  | 7200 |
| Total Polymorphs | 5813 | 69.2 | 7000 | 70. | 79.6 | 8756 | 93.6 | 10863 | 95.2 | 11424 | 94.2 | 18690 | 70 | 5040 |
| Arneth I | 812 | 14. | 1435 | 20.5 | 46 | 4048 | 44.4 | 4839 | 47.2 | 5381 | 47.2 | 8827 | 21 | 1050 |
| " II | 1798 | 31 | 3045 | 43.5 | 36.4 | 3203 | 36.8 | 4011 | 32.4 | 3694 | 30 | 5610 | 33 | 1650 |
| " III | 2320 | 40 | 1855 | 26.5 | 14.8 | 1302 | 13.2 | 1438 | 14.8 | 1687 | 17.6 | 3291 | 34.5 | 1725 |
| " IV & V | 870 | 15 | 665 | 9.5 | 2.8 | 246 | 5.6 | 606 | 5.6 | 638 | 5.2 | 972 | 11.5 | 575 |
| Mononuclears | 2385 | 28.4 | 2760 | 27.6 | 20 | 2022 | 7.4 | 742 | 4.4 | 528 | 5.6 | 1109 | 28. | 2016 |
| Eosinophils | 202 | 2.4 | 240 | 2.4 | — | — | — | — | 0.4 | 48 | — | — | 2 | 144 |
| Mast Cells | — | — | — | — | — | — | — | — | — | — | — | — | — | — |

XI

G.M. 17.2.26 – 18.2.26.

Total Leucocytes.
" Polymorphs.
" Arneth Classes I & II
" " " III, IV & V
" Mononuclears.
Broken line indicates a long interval.

Peptone.
Injection
0.25 ccs.

20000
19000
18000
17000
16000
15000
14000
13000
12000
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000

Hours. after
Injection → 0    1    2    3    4    5    6    7    8    9 — — 24.

TABLE XII.   MACDONALD.   11.3.26.

Peptone 0.8 cc. at 10.30 a.m.

| | 11.3.26 | | 11.3.26 | | 11.3.26 | | 11.3.26 | | 12.3.26 | | 13.3.26 | | 16.3.26 | |
| Date. | 10.30 | | 12 noon | | 3 p.m. | | 6 p.m. | | 10.30 a.m. | | 10.30 a.m. | | 12 noon. | |
| Time. | | | | | | | | | | | | | | |
| Hours after Injection. | 0 | | 1½ | | 3½ | | 6½ | | 24 | | 49 | | 97 | |
| | % | Totals | % | Totals | % | Totals | % | Totals | % | Totals | % | Totals | % | Totals |
| Total Leucocytes | | 8000 | | 6800 | | 10560 | | 20200 | | 10680 | | 7800 | | 10,000 |
| Polymorphs | 64.4 | 5152 | 78.5 | 5338 | 94.8 | 9954 | 97.2 | 19634 | 64.8 | 6934 | 70.8 | 5522 | 62 | 6200 |
| Arneth I | 16 | 832 | 50.5 | 2676 | 49.2 | 4920 | 49.4 | 9682 | 22.5 | 1553 | 13 | 715 | 16.5 | 1023 |
| " II | 32.5 | 1690 | 34.5 | 1829 | 31.6 | 3160 | 29 | 5694 | 39.5 | 2725 | 34 | 1870 | 31.5 | 1953 |
| " III | 38.5 | 2002 | 13.5 | 715 | 14.8 | 1480 | 17.6 | 3450 | 29.5 | 2035 | 40 | 2200 | 42 | 2604 |
| " IV & V. | 13. | 676 | 1.5 | 80 | 4.4 | 440 | 4.0 | 784 | 8.5 | 587 | 13 | 715 | 10 | 620 |
| Mononuclears | 34.4 | 2752 | 20. | 1360 | 5.2 | 546 | 2.8 | 566 | 32.4 | 2466 | 26.8 | 2090 | 36.4 | 3640 |
| Eosinophil | 1.2 | 96 | 1.5 | 102 | - | - | - | - | 2.8 | 300 | 1.2 | 94 | 1.6 | 169 |
| Mast | - | - | | | - | - | | | | | 1.2 | 94 | - | - |
| Myelocytes | | | | | 0.8 | 84 | 1.0 | 202 | 0.4 | 42 | | | | |

XII

J. M. 11·3·26 — 16·3·26.

Peptone.
Injection
0·8 ccs.

Total Leucocytes.

Total Polymorphs.

Arneth classes I & II

Arneth classes III, IV & V

Mononuclears.

Hours after
Injection → 0   1   2   3   4   5   6   7   8   9 — — — 24 — — — 48 — · — · — 96.
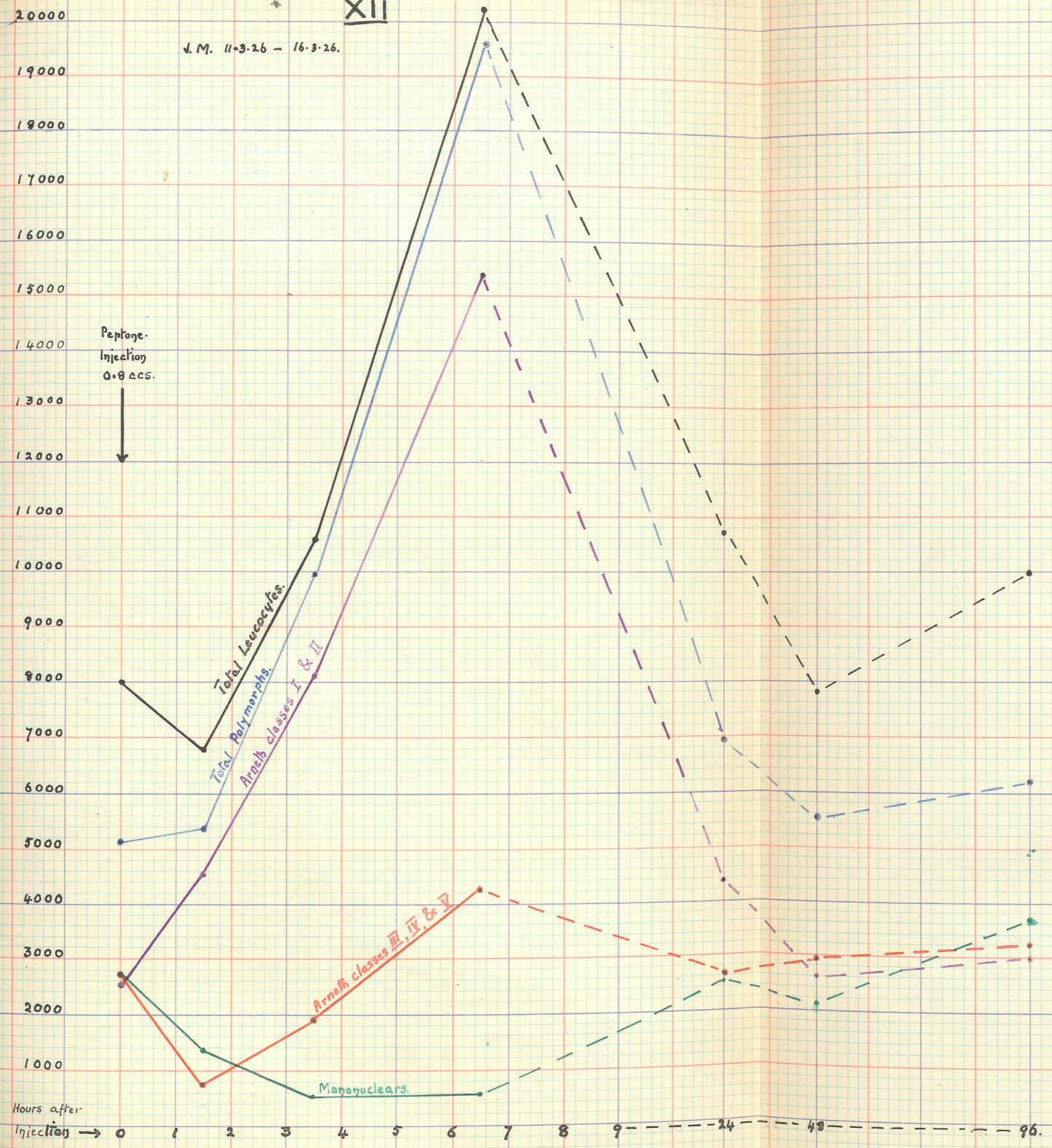
# GENERAL DESCRIPTION OF THE RESULTS OF
# PEPTONE INJECTIONS.

After a peptone injection a general reaction takes place.  Part of this consists in activity of the bone-marrow and this is shown by changes in the leucocytes. Though these changes are part of the general body changes they will be described separately.

## (A)  GENERAL REACTION.

The degree of this reaction varies with the amount of the dose.  The same dose may cause a greater or a less reaction in different patients.  A dose of over 0.8 ccms. will bring about a marked effect in most patients.  Smaller doses may do the same for more susceptible individuals.

From fifteen minutes to half an hour after the injection the patient begins to feel cold.  During this period of chill a headache begins to assert itself. A rigor generally occurs.  The patient feels sick and often vomits.  The temperature rises one or two degrees.  The patient exhibits some degree of cyanosis and suffers respiratory discomfort.  The basal meta-bolic rate is greatly increased.  This stage lasts for a period of half an hour to an hour.

Next/

Next comes a stage of fever. The chill from which the patient has suffered gives place to a feeling of comfort which in turn is displaced by a sensation of excessive warmth and discomfort. The basal metabolic rate is reduced. The temperature rises to $103^{\circ}$ or $104^{\circ}$ Fahrenheit and the pulse rate becomes more rapid in proportion to the temperature. The patient may have pains in various parts of the body. Some have complained of great pain in the small of the back. The joints which are the seat of the Rheumatoid changes usually become more swollen and tender and lose some degree of flexion. This stage lasts for about three hours and ends with more or less profuse perspiration.

During the next few hours all the symptoms gradually abate and at the end of twelve hours the patient is generally as comfortable as he or she may have been before the injection. Sometimes the headache persists for a longer period. The joints which were tender become less so and more supple than they were before the injection. This improvement may not be equal in all the joints. It persists for a few days and succeeding injections increase the movement.

(B) CHANGES IN THE LEUCOCYTES.

(a) Leucopenia. occurs during the period of chill. The total number of leucocytes in each cubic millimetre/

millimetre of blood is reduced by two to three thousand.
The degree of leucopenia seems to depend on the dose.
The smaller doses may not cause any leucopenia or the
decrease in number may be so slight and transient that
it escapes notice.

(b) Leucocytosis follows the leucopenia. It
commences shortly after the rise of temperature begins,
and persists long after the temperature begins to fall.
It may continue for as long as forty-eight hours.
The greatest increase occurs between the sixth and
ninth hours after injection. The rise is rapid and
the fall gradual.

(c) The Differential Leucocyte count shows that
the different varieties are unequally affected.

During the period of leucopenia all varieties
are decreased in total number but there is not a very
great change in the percentages. If the blood specimen
is taken after the lowest point of the leucopenia a
relative neutrophil increase may be seen because the
leucocytosis has really commenced. Sometimes during
the leucopenia there is a relative decrease in
polymorphs as in the case of G.M. in table III and
graph III.

Neutrophil Polymorphs make up the bulk of the
leucocytosis. As the graphs and tables show there
is a decided increase in the cells of Arneth Classes
I/

I and II.   This corresponds to a shift to the left.

The <u>Eosinophils</u>  are decreased in numbers.
As a rule they are only slightly diminished in numbers
during the leucopenia.  After that they are seldom
found till the day after injection.

<u>Mast Cells</u>  behave in the same way as the eosino-
phils.

<u>Mononuclears</u>  decrease in number during the
leucopenia.  A further diminution in their numbers may
occur during the leucocytosis.  But when the total
number of the white blood cells begins to decrease
after the height of the increase the mononuclears
increase in number both relatively and absolutely.
At the end of the leucocytosis the total number of
mononuclears may be greater than it was before the
injection.

In one case (G.M.  table II and graph II) the
mononuclears show an increase during the height of the
leucocytosis.   This will be discussed later in con-
nection with promyelocytes.

<u>Neutrophil Myelocytes</u>  are found during the
height of the leucocytosis.

<u>Premyelocytes</u>.   Their appearance in the peri-
pheral blood will be discussed later.

## COMPARISON OF THE AFOREMENTIONED RESULTS WITH
## THOSE OF OTHER OBSERVERS.

(a) General Reaction.

Many investigators have recorded
the results of intravenous injections of peptone and
other allied protein substances, (such as those de-
rived from bacteria) or of the intravenous injection
of metallic preparations.   Macfarlane and Barlow[2]
have used peptones in Asthma and Rheumatoid Arthritis;
Auld[3] has published the results of similar work.
Scully[4] has used Typhoid vaccine in Acute Articular
Rheumatism, Chronic Rheumatoid Arthritis, and Lobar
Pneumonia.   Gay and Chickering[5] have employed
"a ground polyvalent vaccine that had been sensitised
by Antityphoid serum, and then killed and precipitated
with alcohol.  From the ground culture the endotoxins
were extracted by carbolated saline solution and the
remaining sediment of bacterial bodies alone were
used."   Auld[6] has also employed colloidal metals
and found that the body reacts in the same way as
when a protein derivative is injected.

These observers are in singular agreement with
regard to the clinical and other phenomena which have
occurred after their injections·  And to state their
findings would be to restate what has already been
written earlier in this thesis·   One worker may omit
one/

# XIII

Composite curve from 47 injections in 25 cases.
Typhoid Vaccine used in Rheumatic Fever.

compiled from article by SCULLY.
Journal of the American Medical Association
1917 (69) p 20.



Leucocytes    Temperature.

Injection

40000 105°F
35000 104°
30000 103°
25000 102°
20000 101°
15000 100°
10000 99°
5000 98°

Total Leucocytes.

Temperature.

Hours after Injection → 0    3    6    9    12         24                    48.
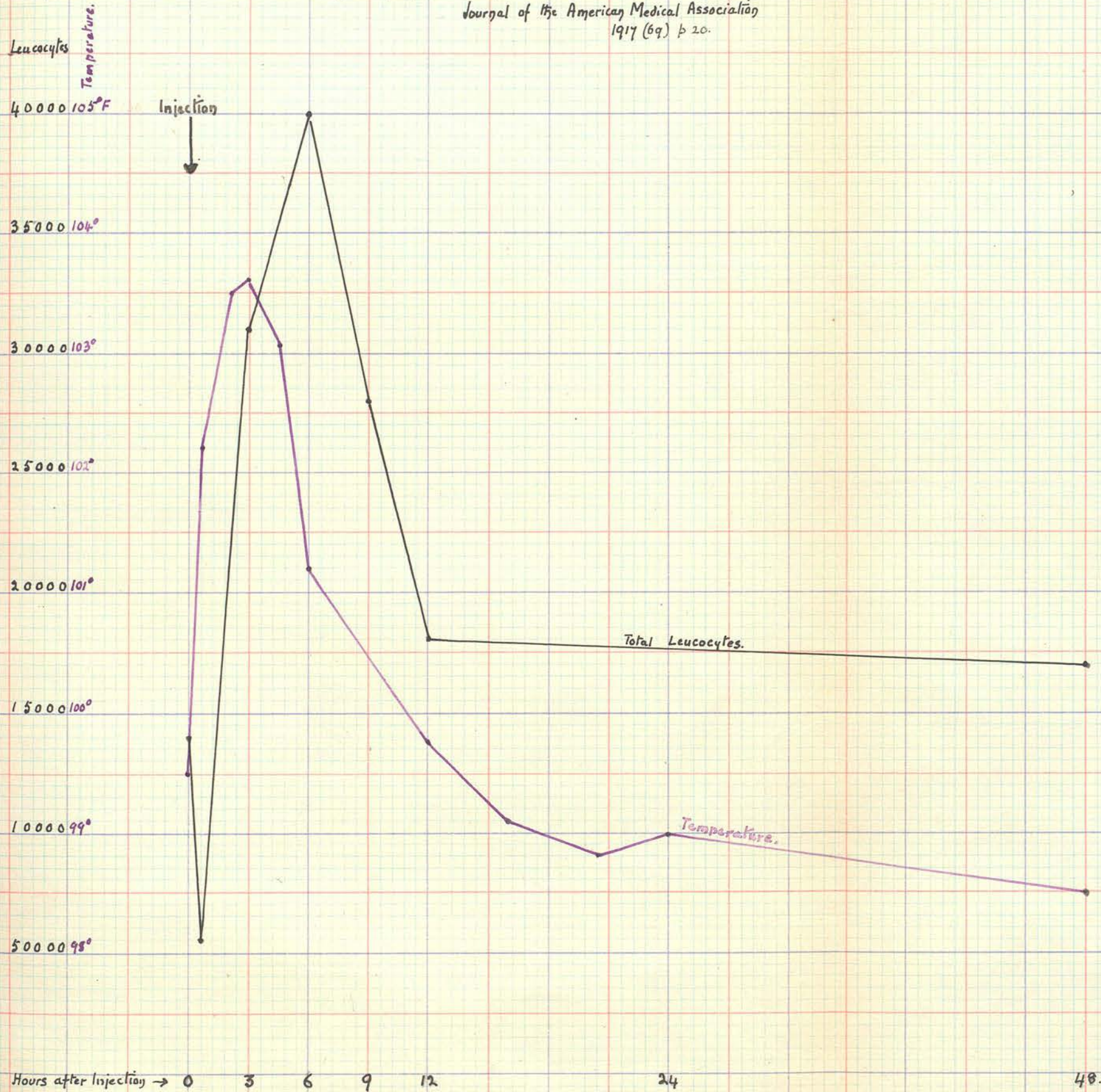
Small Lymphocytes show a slight rise during the chill followed by a fall after two to three hours; and then a gradual rise to the same percentage as before.

Eosinophils show an absolute and relative increase followed by an absolute and relative decrease.

Basophils show an absolute and relative increase followed by an absolute and relative decrease."

Most of the other observers are content to record a neutrophil leucocytosis.

My findings do not agree with Scully's with regard to the Basophils. They seem to me to follow the same numerical variations as the Eosinophils. They were sometimes present during the whole of the leucocytosis. On other occasions they were present at some period of the leucocytosis but their appearance at any particular period was inconstant. In this my results agree with those of Gulland and Goodall[7], who, in describing a neutrophil leucocytosis state: "Eosinophils and Basophils are often absent or reduced to a minimum, especially in septic cases." So apparently the laws to which they conform are not yet discovered.

Auld[6], Elliot Smith[8] and Fergusson & Thomas[9] record the results of the injection of metallic and other preparations. Auld employed intravenous injections of colloids of platinum and of gold. Elliot Smith and/

and Fergusson & Thomas[9] used intramuscular injections
of one gramme of the Salicylate of Mercury, or 0.5
grammes of Quinine Bihydrochloride, or intravenous
injections of Novarsenobilon.

Auld found that a similar general reaction and a
similar neutrophil leucocytosis occurred. In the two
instances in which I observed the results of intra-
venous Sanocrysin injections, the general disturbance
was slight, and the neutrophil increase was not very
marked. In this point I agree with Fergusson & Thomas[9]
who noted that in the leucocytosis following an intra-
muscular injection of the Salicylate of Mercury the
variations in the differential count were within the
normal limits.

One of my two counts after a Sanocrysin injection
showed a polymorphonuclear percentage above seventy-
five and then it was only seventy-nine. On this
occasion no estimations were made between the periods
of $3\frac{1}{2}$ and $7\frac{1}{2}$ hours after injection. It is possible
that the height of the leucocytosis occurred in the
interval for the polymorph percentage of 79 was found
when the leucocytosis had passed off. (Table number
IX). The observations are too few to permit of a
general statement. They have been included for the
sake of their agreement in the Arneth variations.

(c)/

(c)   Arneth's Classification.

As regards this class-
ification I have not been able to find references to
any series of counts made during the development of a
neutrophil leucocytosis.  The nearest related series
of figures is that published by Cooke.[1]   He has made
counts by this method in a variety of diseases such
as Typhoid Fever, Measles, Scarlet Fever, Erysipelas,
Diphtheria, Rubella, Chicken pox, Whooping Cough and
Gonorrhoea.   In each count there is a shift to the
left.   Rayevsky[10] and others have shown a shift to the
left in cases of Tubercular infection.  Now some of
these diseases show a neutrophil decrease, others show
no marked change in total numbers, others show a
neutrophil increase.  This is in agreement with my
records which show a shift to the left even during
the period of leucopenia; also in the Sanocrysin cases in
which the differential count does not show much
variation from the normal; and in the counts in which
there is a great neutrophil increase.

Cooke, Rayevsky,[10]  and Kramer (quoted by Rayevsky)
are in general agreement with Arneth in regard to the
percentages in which the various Arneth classes are
to be found in normal individuals.  An average of
my basal counts which were made before the injections
does not vary greatly from their figures.

I have also made a number of counts in such
diseases/

diseases as Pneumonia, Endocarditis, Septicaemia,
Acute Rheumatic Fever, and Broncho Pneumonia.  These
counts, as well as those made after the peptone in-
jections, agree with Cooke's.   Those made after
peptone show a greater deviation to the left than any
of Cooke's figures.  Perhaps this is because the
leucocytosis was more sudden and transitory.  Cooke's
estimations would be made after a more settled leuco-
cytosis had been established.

The following are the normal averages in per-
centages as found by Arneth, Cooke, Rayevsky and
Kramer, together with an average from my basal counts:-

|  | Class I | Class II · | Class III | Class IV | Class V |
|---|---|---|---|---|---|
| Arneth | 5 | 35 | 41 | 17 | 2 |
| Cooke | 10·9 | 25 | 46·7 | 15·3 | 2·1 |
| Rayevsky | 5·33 | 34·74 | 42 | 15·5 | 2·33 |
| Kramer | 4 | 30 | 45 | 18 | 3 |
| Average of my basal counts. | 10·4 | 28·5 | 43·6 | 14 | 3·5 |

This shows that the basal counts are very like the
normal average.   I have omitted two counts which
showed such an obvious shift to the left that they
could not be considered even approximately normal.

Cooke's/

Cooke's figures for various diseases are as follows:-

|  | Class I | Class II | Class III | Class IV | Class V |
|---|---|---|---|---|---|
| Typhoid Fever | 43-54 | 31-33 | 13-22 | 0-5 | 0 |
| Scarlet Fever | 26-44 | 32-43 | 13-30 | 2-8 | 0-1 |
| Measles | 39-51 | 30-39 | 14-20 | 1-3 | 0-1 |
| Erysipelas | 44-59 | 30-40 | 6-19 | 0-1 | 0 |
| Diphtheria | 21-60 | 32-48 | 8-32 | 0-5 | 0-1 |
| Rubella | 22-30 | 30-35 | 32-43 | 3-4 | 0-4 |
| Chicken Pox | 18-51 | 31-35 | 17-45 | 1-6 | 0 |
| Whooping Cough | 24-34 | 39-44 | 27-31 | 0-3 | 0 |
| Gonorrhoea | 12-20 | 31-30 | 39-43 | 8-12 | 1 |

A  DISCUSSION  OF  THE  MEANING  OF THESE OBSERVATIONS.

(A)  The General Reaction.

This bears a strong resemblance to an attack of Malaria.  In each case the typical sequence of events is a cold stage followed by fever which abates gradually.

The injection of a dose of peptone corresponds to/

to the process of sporulation in an attack of Malaria.
In each case a feeling of discomfort follows. This
develops into a chilly feeling which may end in a
rigor. During this cold stage the skin temperature
falls though the rectal temperature may be rising.
The patient looks blue. The pulse is rapid, the
peripheral arteries contracted. Nausea is present.
Vomiting may occur at this stage or early in the next.
In some cases of Malaria no cold stage occurs, and
sometimes after injections of peptone too the period
of fever is not ushered in by a chill or rigor. This
stage lasts for twenty or thirty minutes.

A period of fever follows both in Malaria and
after an injection of Peptone. Headache is common
to the two conditions. The pulse becomes full and
bounding and the pulse-pressure is reduced. During
an attack of Malaria the patient may become delirious.
Great mental distress sometimes occurs after a peptone
injection.

After the fever has lasted for from three to
five hours the patient begins to perspire. The
temperature then begins to fall and all the symptoms
abate. The headache often lasts longer than the fever.

If an acute infectious fever like Measles could
be compressed into the space of a day, the resemblance
would also be close. Many cases of Liver Abscess,
atypical cases of Typhoid or Paratyphoid fever have
days/

days in which a similar sequence of events occurs.

In each case a foreign substance has entered the body of the sufferer.   There is the obvious difference that in the case of Malaria or of an infectious fever the foreign substance is a living one.   Typhoid vaccine as used by Scully, and ground bacteria as used by Chickering and Gay provide links between the living plasmodia or bacteria and the protein derivatives which compose Armour's peptone.

Moreover the foreign substance or antigen in each case causes the reaction when it is in the blood stream.   The plasmodium of Malaria causes no fever until sporulation occurs.   It is only then that the parasites are free in the blood.   When they become attached to or penetrate erythrocytes, or suffer destruction from the attacks of leucocytes or quinine or fixed tissue cells, the fever begins to abate. Few observers have the temerity to describe the free forms of the plasmodium.   When an object that looks like a merozoite is unattached to a red corpuscle there is always considerable doubt as to its identity. Nevertheless the young parasite must spend some time free in the blood stream.   And as fever only follows sporulation it is fair to conclude that there is a causal connection between this freedom of the merozoites and the pyrexia.   In the case of bacteria general symptoms are produced when they or their toxins enter the/

the circulation.    Tubercle bacilli when encysted in
a fibrous capsule cause no symptoms.    In the same way
metals do not affect the body as a whole till they
enter the circulation.    A sterile metal plate fixed
to a bone causes no symptoms; nor does an intramuscular
injection of Mercury.    Instances could easily be
multiplied to support this contention.    But for the
purposes of this thesis it is enough to establish the
fact that the intravenous injection of "peptone"
produces a reaction that is very similar to those
caused by living substances free in the blood stream.

The similarity of the reaction tempts one to
consider the possibility that living parasites and
bacteria only produce their effects when they dis-
integrate and that protein derivatives are the actual
cause of the reaction.    It is even possible to argue
that metallic and other foreign substances act in the
same way by causing the degeneration of tissue cells
and so producing peptones.    The lack of experimental
evidence takes away the possible usefulness of such
speculation though it is deeply concerned with the
rationale of non-specific protein therapy.

In an earlier part of this thesis attention was
called to the agreement of the various observers on
matters of fact concerning the results of protein and
other injections.    This does not produce any unanimity
with regard to the theories put forward to explain
the /

the findings.   Nor is there any agreement as to the manner in which the injections of vaccines, bacteria, protein derivatives and inorganic compounds help to cure or alleviate such a variety of diseases as Typhoid Fever (Gay and Chickering), Acute Rheumatic Fever, Lobar Pneumonia, Chronic Rheumatism (Scully), Asthma, Chronic Rheumatoid Arthritis (Macfarlane and Barlow) - and the list is not exhausted.   Whatever be the mechanism, the symptoms, which have been described, are always present in some degree.   They are produced during the body's attempt to attain immunity from a foreign substance, - that is - the body's attempt to absorb, confine, or extrude its unwelcome visitors.

This comparison of the effects of a peptone injection with Malaria and other conditions has been made to show that the similarity of symptoms suggests that the same mechanism carries on the struggle for immunity, whether the antigen is a living organism or is merely a chemical entity.   This point needs to be kept in mind during the consideration of the leucocytic reaction.

B.   Leucocytic Reaction.

The changes we have to consider are those stated in a previous section of this thesis.   They may be summarised briefly as follows:-

(1)/

(1)  An initial leucopenia affects all varieties
     of cells.

(2)  A Neutrophil leucocytosis follows.

(3)  The Arneth Count shows a progressive shift to
     the left during the leucocytosis.  This shift
     to the left is seen even during the period of
     leucopenia.

(4)  The mononuclear cells decrease during the
     leucocytosis and increase gradually after the
     height of the leucocytosis.  There is occasion-
     ally a mononuclear increase during the height
     of the leucocytosis.

The ages of the Cells in Arneth's Classes.

Arneth claims that polymorph cells of Class I are
the youngest cells and those of Class V the oldest
polymorphs.  This has been disputed by observers who
state that some of the cells of Class I with rounded
nuclei are really degenerated forms.  These conflict-
ing views must be considered before the other leucocyte
changes can be discussed.

Arneth's classification depends on the nuclei of
the polymorphs so we will first consider it from the
point of view of the development of the neutrophil
nucleus.  We do not need to go far back in its evolution.
The neutrophil myelocyte is typically a cell with an
oval kidney or horse shoe shaped nucleus.  This  horse
shoe/

shoe shaped nucleus is the immediate precursor of the
nucleus of the polymorph as we meet it in the peri-
pheral circulation.  The nuclei of cells in Arneth's
Class I very closely resemble the horse shoe myelocyte
nuclei.  The most complicated nucleus of this class
consists of a series of segments attached to each
other by bands of nuclear matter.  Transitional forms
can be seen which link together all the members of
the series of classes.  In class I we find cells
with nuclei like horse shoes, ribbon like nuclei with
no nodes, twisted ribbons, ribbons with nodes on them.
These are succeeded by the bilobed nuclei of class II,
which in turn give place to classes III, IV and V.
And it is not necessary to look at pathological speci-
mens to find these cells; they are present in the
blood of healthy individuals.  The resemblance be-
tween those of the cells of class I which have the
most simple nuclei and the myelocytes with horse shoe
shaped nuclei is so close that it is a matter of
difficulty to place the one in one category and the
other in a different one.  The gradual changes in the
nuclei are shown more or less diagramatically below.

Myelocyte.

Class I
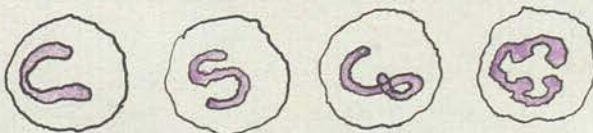
Class II
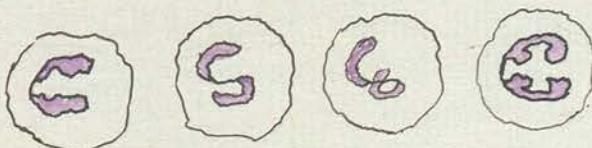
Class III
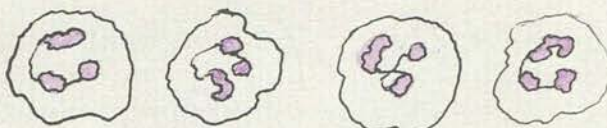
Class IV
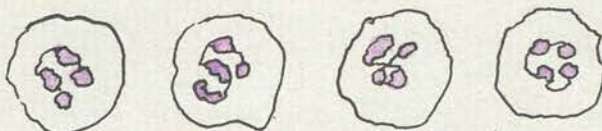
Class V
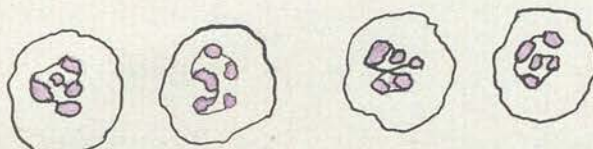
M. Heidenheim explains the development of the
horse shoe shaped nucleus from the rounded form by a
reference to the behaviour of the nucleus and centro-
some.    Embedded in the cytoplasm of a free cell are
radii which proceed outwards from the centrosome.
These radii tend to pull the centrosome to the centre
of the cell.    In so doing they displace the nucleus
if the relative sizes of the cell and the nucleus
allow of this.    The nucleus is thus pushed to one
side and deformed.    Pappenheim explains the further
development of a polymorph nucleus as a process of
ripening.    Gulland and Goodall[7] suggest that this
process is for the purpose of facilitating amoeboid
movement.    Pappenheim also considers that the changes
in the nucleus are not reversible.    Once a nucleus
is divided into lobes it remains divided or can be
still further segmented but it cannot again regain
the/

the simple horse shoe shape.    This means that cells
of classes II, III, IV and V  are, in that order,
further removed from myelocytes than the cells of
Class I.

It is possible that the nuclei of cells do not
alter while the cells are in circulation and that
they complete their lives in the state in which they
first left the bone marrow.    Such a view would make
it possible for any class to contain cells of all
ages.    But such a view would not take any account of
the time spent in development in the bone marrow.
It is fair to assume that the cells of more advanced
development take a longer time to ripen than those
less advanced.    The time taken for this preparation
of the nucleus would need to be considered in deter-
mining the age of a cell.    If Arneth's classification
were considered from this point of view, it would be
a differentiation of cells in accordance with the
stage of development of their nuclei.    There would
be a distinction but no real difference between such
a statement and Arneth's original one.

Before Pappenheim put forward his explanation of
the form assumed by the Polymorph nucleus, the
accepted theory was that the nucleus became deformed
as the result of the cells amoeboid movements.  This
theory too is in favour of the less complicated nuclei
marking the younger or, at any rate, the cells that
had/

had shown least activity.   The classification would
then indicate intensity rather than length of life.

Carnegie Dickson[11] in describing the development
of the neutrophil polymorph states:-  "As this trans-
ition from myelocyte to adult leucocyte takes place,
the nucleus becomes progressively more and more con-
voluted and irregular in shape until it finally
assumes the typical and familiar type found in the
polymorphonuclear leucocyte".   He was not contem-
plating Arneth's classification and so it is not fair
to stretch his meaning.   Nevertheless his description
does describe a progress from a simple to a more
complicated type of nucleus as being part of develop-
ment.

I have not been able to find any reference to a
neutrophil leucocytosis which failed to show a shift
to the left.   Nor have I examined any blood film taken
during the course of a polymorph leucocytosis which
did not show a drift to the left.   Other observers,
already quoted, have demonstrated its occurrence in
many conditions.

The successive counts made during the development
of a leucocytosis following a peptone injection show
a progressive increase in percentages and absolute
values of Classes  I and II.   The neutrophil in-
crease is almost wholly made up of cells of these
classes, as the graphs show.  If we were to consider
the cells of class I as degenerate forms then we
would/

would have to go further and state that large numbers
of degenerate forms are produced by the bone marrow
for the purpose of combating toxic conditions.
Or we would have to assume that a depot of veteran
leucocytes is maintained for a leucocytosis.   The
first of these statements is not in accordance with
the efficiency of the body machine nor even with the
ability of a leucocytosis to achieve its purpose.
The second assumes an arrangement which has no
parallel in the body nor has any one described such
stores of cells in the bone marrow.   And there is
no doubt that a neutrophil leucocytosis is the pro-
duct of bone marrow activity.

We find then (1) that morphologically the nuclei
of the cells of Class I more nearly resemble the
nuclei of myelocytes than do those of Class II, and
that classes III, IV and V  show a progressively more
distant likeness to the myelocyte; (2) that the
segmentation of the nucleus is the result of develop-
ment; (3) that the cells of Classes I and II represent
the bulk of the result of bone marrow activity during
a leucocytosis.   Both facts and theory force us to
agree with Arneth with regard to the ages of the cells
in the different classes.

The Leucopenia that occurs shortly after the
injection of peptones now has to be considered.

The leucopenia affects all types of cells.
What/

What causes it?

Not all cases showed the initial leucopenia.
It is possible that sometimes it did occur but was not
found because the interval between the injection and
the taking of the first specimen of blood was too
lengthy.  But that its occurrence is not invariable
will be seen by reference to graphs X and XI.  These
were both made from the same patient on different
occasions.  On the first occasion the dose was only
0.25 ccs. of peptone and no leucopenia occurred.
A count made half an hour after the injection showed
the beginning of a leucocytosis.  On the second
occasion the dose was 0.8 ccs. of peptone and a leuco-
penia was found as long as one and a half hours after
the injection.  So the dose has something to do with
the nature of the reaction and this is in conformity
with the general observation that drugs which stimulate
in small doses often depress if they are used in large
doses.  We will revert to this point after considering
the causes of the leucopenia.

A leucopenia, as we know it, is a reduction in the
number of white blood cells in the peripheral circula-
tion.  This does not of necessity mean that there is
a reduction in the total number of cells in the body.

There are two possible ways in which a leucopenia
may be brought about.

(1)  It may be the result of a redistribution of
     corpuscles in the body.

(2)/

(2)  It may be due to the destruction of corpuscles.

These two possibilities must be considered in turn.
Various observers[12] have found that in health leucocytes
are not evenly distributed throughout the body.  The
spleen, liver, kidneys and bone marrow have more,
other internal organs and the central blood vessels
have less than the proportion in the peripheral
circulation.  It is possible that a leucopenia is
an exaggeration of this unequal distribution and that
there is a concentration of cells in some of the
internal organs.

Teale[13] has published the results of some interest-
ing experiments that have a bearing on this point.
He injected sometimes virulent and at other times non-
virulent bacteria or spores into a vein of an immune
or a susceptible animal.  A minute after the injection
he drew blood from another vein and after culture
counted the colonies recovered.  He repeated the
drawing of blood and making of cultures at intervals for
a period of 48 hours.  The number of colonies re-
covered 1 minute after injection varied from 50,000
to 800,000; after an hour only, 300 to 3000 were
recovered; after four hours the numbers varied from
40 to 600; after 48 hours, if the animal survived as
long, no colonies were recovered.  The result was
the same whether he used immune animals or not, whether
the/

the bacteria were virulent or harmless. Even spores
were removed from the peripheral circulation with the
same speed. Now though the organisms could not be
found in the circulation they could be demonstrated
in the capillaries of the lungs, liver, spleen and
bone marrow. Phagocytosis took place in those sites
by means of leucocytes and also by means of the local
fixed tissue cells. The disappearance of the bacteria
did not depend upon antibodies for it took place with
the same rapidity in immune and susceptible animals.
The bacteria were found in clumps entangled in masses
of blood platelets and gelatinous material which he
considered might have been incipient fibrin.

Any foreign substance injected into a vein has
to follow the direction of the blood stream in the same
way as the bacteria of Teale's experiments. Such
substances proceed through the right side of the heart
to the lungs and on to the left side of the heart.
Thence they complete the circuit through the body.
This goes on over and over until the peptones are
excreted, hydrolysed or neutralized in some way.

After a meal containing protein, amino-acids
enter the blood stream and give rise to no untoward
symptoms. If peptones injected into the blood stream
were further hydrolysed they would be rendered in-
nocuous. Halliburton [14] refers to some experiments
by Mendell and Rockwood. They injected foreign food
proteins/

proteins intravenously and intraperitoneally. These proteins were apparently used in the body. In some cases small quantities of proteoses were found in the urine. They concluded that the proteins had been broken down by tissue cells. The enzymes in these cells are capable of doing the work of Trypsin and Erepsin.

Is it possible that the peptone molecules are detained in the lungs, liver, spleen and bone marrow in the same way as the bacteria of Teale's experiments?[13] And do they lodge in the damaged tissues of the affected joints in Rheumatoid Arthritis? The experiments of Mendell and Rockwood[14] show that the peptone must lodge somewhere to be split up by the tissue cells. Normally the liver deals with the excess of the amino-acids of digestion. The same organ may deal with the more complex peptones. We do know that the bone marrow is stimulated, and that the heat regulating centres are affected. So we may conclude that the peptone molecule forms chemical combinations or becomes attached to cells in various parts of the body. If so, would they cause local hyperaemia and leuco-cytosis and so produce a leucopenia in the Peripheral blood? It is probable that they do. Dale[15] states that the leucopenia is due to leucocytes adhering to the walls of capillaries. As a result they are not found in the circulation. (I have not been able/

able to verify the reference so I am not able to state whether Dale was referring to capillaries in general or to those of any particular organ.   Nor have I been able to find references to any animal experiments on this point).

The second possibility is that the leucopenia is caused by the destruction of leucocytes.  We have to explain the deficiency in the number of leucocytes during the initial leucopenia and also the more gradual reduction of much larger numbers when the leucocytosis ends and a restoration to normal takes place.

During health leucocytes like other body cells are formed, employed, and destroyed.   My conception of the life of leucocytes is that some enter the circulation as cells of Arneth's class I, some of class II.   In the circulation they develop into cells of the other classes.   Not all the cells reach full maturity, many are expended or killed before full ripeness is attained.   During the course of  a  day many slight infections occur and small doses of toxin have to be neutralised.   The normal number of leucocytes is sufficient for this.  Those that are destroyed during the wear and tear of the day are replaced by freshly formed cells.   If some such gradual destruc- tion did not take place the various Arneth classes would contain approximately equal numbers of cells. The/

The comparison of this age distribution to that of a normal human population has already been made. We can complete it by suggesting that it is produced by a similar method of elimination. Cells and men at the extremes of life have a greater expectation of death.

If this is so, then during the return to normal conditions at the end of a leucocytosis cells of classes I and II would be developing into cells of classes III, IV and V, but this would not account for all the cells that disappear from the circulation. Are these young cells more delicate than those of the more developed classes, and are they destroyed more quickly? The restoration to normal is very gradual, so no sudden holocaust has to be assumed. Dale's statement that leucocytes adhere to the walls of capillaries is certainly not against the possibility of destruction. There must be some alteration in the endothelium of the capillaries, or in the cell membrane of the leucocytes, or in both to cause such an adherence.

In favour of the possibility of the destruction of leucocytes is the theory that ferments and anti-bodies are produced by the disintegration of leucocytes. This is not yet proven. Wright's [16] first case of immuno-transfusion proves that antibodies (or some substances of an allied nature) are manufactured in the/

the blood and are independent of fixed tissue cells.
In this case a vaccine was added to a litre of the
donor's blood which was stored in a suitable paraffin
coated vessel.   After this had been allowed to in-
cubate for some hours it was transfused into the
patient who recovered from a very critical condition.
No record was made of the condition of the leucocytes
at any stage of the process; so that, though the
production of opsonins, ferments or antibodies is
proved, no evidence is brought forward to show that
the leucocytes broke down to manufacture them.
However there is a strong presumption that the only
cells present in the blood must have been the causal
agents.

Another point in favour of the destruction of
leucocytes during leucopenia is the shift to the left
reported by Cooke[1] in cases of Typhoid Fever.   The
shift to the left indicates that the bone marrow is
producing fresh polymorphs.   In spite of this the
leucopenia in Typhoid fever mainly affects the poly-
morphs.   What is happening to these polymorphs?
Destruction or redistribution are both possible.
The severity of the disease, its long course, the loss
of the patient's weight, the parenchymatous degenera-
tion in organs like the liver and kidney , all incline
one to think that destruction is taking place.

The evidence is not conclusive, and the question
must/

must be left open.    Probably both processes are in
action at the same time, a redistribution of cells
takes place, and great numbers of cells are destroyed.


## THE  PERIOD  OF  LEUCOCYTOSIS.

A leucocytosis is an
increase in the number of white blood corpuscles.
In practice we only estimate the number of the white
blood cells in the peripheral circulation and take no
account of a possible redistribution of cells.  As we
have seen in the occurrence of a leucopenia this has
to be borne in mind.   Gulland & Goodall[7] point out
that sometimes when an abundant polymorph leucocytosis
occurs before death no signs of it are present in the
bone marrow.   They suggest that this is due to a
terminal sweeping out of the cells in the marrow.
A possible additional explanation is a redistribution
of cells due to other organs like the liver, spleen,
and kidneys as well as the marrow giving up the leuco-
cytes that were concentrated in them.  But such a
condition is exceptional.  It is not sufficient to
make us doubt that a polymorph leucocytosis indicates
bone marrow activity.

But does the measure of a leucocytosis represent
the whole of the activity of the marrow?    As we have
seen an initial leucopenia occurs and this is caused
by/

by a redistribution or destruction of leucocytes or
a combination of these processes.    Redistribution is
due to the positive chemiotaxis of the peptone which
is concentrated in the liver or spleen or bone marrow,
or in all these organs.    If we favour the theory of
destruction we must assume that it is caused by the
peptone that has been introduced into the circulation.
In either case we must grant that the process of re-
distribution or destruction will continue as long as
the peptone is not neutralized, and the body has not
gained immunity.

One of the signs that an antigen is taking effect
is the general reaction.    In the case of a patient
suffering from Pneumonia or other disease due to
bacteria the reaction goes on for days because there
is a continued production of toxins.    In the case of
a single peptone injection the pyrexia only continues
for a few hours because the peptone is rapidly
neutralised and the dose is limited.    Vaughan[17]  has
shown that by repeated daily injections protein fever
can be continued for weeks and that the temperature
curve in such a case is indistinguishable from that
of Typhoid Fever.    With the limited doses which are
generally used the fever abates as soon as the body
gains immunity.    But the leucocytosis continues and
even increases while the temperature is falling.
And not only does the leucocytosis increase but the
shift/

shift to the left in Arneth's count becomes more
marked until the fall in the number of white blood
cells commences.

Does this mean that the bone marrow is unable to
cease its activity as rapidly as the other mechanisms
of the body are able to settle down after their dis-
turbance?    Or does it mean that the clinical symptoms
require a greater minimal stimulus than the bone
marrow?    The latter is probably the true explanation.
That a variable minimum quantity of a drug or a toxin
or bacteria is required to evoke a general reaction is
well recognised.    That the continuance of the symptoms
depends on the continued presence of a minimum quantity
of the stimulant is also well known.    In describing
the crisis of Pneumonia, Osler & Macrae [18] write:-
"The crisis, the most remarkable phenomenon of pneu-
monia, appears to represent the stage of active
immunity to the toxin of the pneumococcus.    The fever,
dyspnoea, and general symptoms disappear when the
immunity reaches a certain stage".    After the crisis
in Pneumonia the bacteria are still present in the
lung.    They may even cause complications later.
The point is that at the time of the crisis, the
concentration of toxins is below that necessary for
the continuance of the fever.    So too after a peptone
injection the subsidence of the general symptoms means
that the remaining quantity of peptone is too small to
evoke them.    This fact does not provide sufficient
foundation/

foundation for the assertion that the leucocytosis is
continued to complete the victory over the peptone.
But we may say that such an arrangement is very pro-
bable.

We can now return to the question as to whether
a leucocytosis as measured in the ordinary way re-
presents the whole of the bone marrow activity?
Most assuredly it does not.   As we have seen Leuco-
penia is caused by the redistribution or destruction
of leucocytes by the action of peptone.   Let us
connect this with the other fact that the general
symptoms of fever and its accompaniments indicate the
active stage of the peptone.   We can then state that
the process of redistribution or destruction or the
combination of the two must continue as long as the
general symptoms last.   Therefore, in spite of the
increase in the number of leucocytes in the peripheral
circulation, large numbers of white blood cells are
being destroyed or concentrated in certain organs
of the body.   That this is true can be shown from a
comparison of the well known facts of pneumonia.
In this disease we know that there is an enormous
concentration of leucocytes in the affected part of
the lung and in spite of this the number of polymorphs
in the peripheral circulation is increased.

In this connection further evidence is offered
by the Arneth count.   The shift to the left is
evident even during the initial leucopenia.   This
shift/

shift to the left, as we have seen, indicates increased
bone marrow activity.    In other words the leucocytosis
has commenced but is not evident because it is masked
by the leucopenia.    It only becomes evident after
the increase of white cells is in excess of the de-
crease that has occurred.

From a consideration of these arguments we may
conclude that the leucocytosis which can be measured
in the peripheral circulation only represents part of
what is occurring.    A great number of the fresh cells
that are being produced by the bone marrow are being
used to deal with the peptone in the liver, lungs,
kidneys and spleen.    The two processes of production
and concentration or destruction are going on at the
same time.    The measured leucocytosis only represents
the difference between the total product of the bone
marrow and that proportion which is being expended in
neutralizing the antigen.

If then a leucocytosis is very high, it means
that though the marrow is very active the toxins to be
combated are present in large quantities or are very
intense in their virulence.

If we get the combination of a slight leucocytosis
or a leucopenia with severe general symptoms and a
marked shift to the left of the Arneth count, we may
conclude that the bone marrow is acting vigorously,
but that the processes of redistribution or destruction
are more active still.    This is shown in Cooke's[1]
figures/

figures for Typhoid Fever which are given in another part of this thesis.

The practical result of such a view is that in such cases we need to neutralize the toxins in some way.    Chickering & Gay[5] have used vaccines to produce a leucocytosis in Typhoid Fever.    They claim that distinct benefit resulted in 66% of their cases but their figures are not very convincing.    Possibly this is because they were whipping a tired horse. Theoretically some such procedure as immuno-transfusion would be more efficacious.    Such a method would reduce the load against which the bone marrow was working, instead of stimulating the marrow to make greater efforts.

## THE   ARNETH   COUNT   IN   PROGNOSIS.

The following remarks only arise out of what has gone before in this thesis.    As I have no actual ex-perience of the use of the Arneth Count in disease, my suggestions are only theoretical.

Arneth claims that the degree of the shift to the left indicates the degree of the patient's resistance.

The various graphs illustrating the shift to the left show that it is parallel to the degree of leuco-cytosis/

leucocytosis except during the period of leucopenia.
An isolated count, taken at the beginning of a leuco-
cytosis might show only a slight shift, but to give
a good prognosis on that would be erroneous as the
patient's troubles would be all to come.

An isolated count at the beginning of a fall in
leucocytosis would show a marked shift to the left
and if this were to prompt a bad prognosis, the
opinion would again be erroneous.  Such isolated
counts only indicate that the bone-marrow is or has
recently been active.

In an acute condition a succession of counts
would show whether the bone-marrow was increasing or
decreasing its efforts.  But an ordinary white cell
count would show that with greater accuracy, except
in those cases in which no great increase of leucocytes
occurred.  One of my cases gives an instance of this.
In table III the total count at 3.10 p.m. was slightly
greater than that which was found at 4.20 p.m.
I thought that the height of the leucocytosis was over,
but a count done at 7 p.m. showed I was wrong.
The Arneth count at 4.20 p.m. showed a greater shift
to the left than that at 3.10 p.m.   I did not appreciate
the significance of this at the time and made no dif-
ferential count in the 7 p.m. film.

In conditions like chronic tubercular ~~one's~~ cases
Arneth counts are, as one would expect, very valuable.
In/

In these cases the leucocyte increase is slight or absent. An Arneth Count would show whether new cells were being produced. Arneth claims that a shift to the left indicates the patient's power of resistance. In a sense it does, because it shows in these cases that though the bone marrow is active the number of leucocytes is not increasing. Earlier in this part of the thesis I have tried to show that this means that the cells are being expended as fast or faster than they are being produced. Hence if successive counts are made, with an interval of a few days between them, an increase of the dislocation to the left would be a bad sign. A decrease would be a good sign.

Arneth states that the younger cells are less able to combat infection than the old and that therefore a shift to the left indicates the patient's power of resistance. The conclusion seems correct, but I am not so confident about the reason alleged. My figures seem to suggest that the young cells must be quite efficient. For if every leucocytosis is like that which is produced after peptone, (and this seems likely) then, if young cells could not combat infection the work would have to be done by a diminishing number of old ones. More counts need to be done in series in a large number of different conditions before a definite opinion can be formed on this point.

MONONUCLEARS./

## MONONUCLEARS.

The work I have done was for the purpose of examining the neutrophil variations, and I am not prepared to hazard any opinion with regard to the mononuclears. And yet their variations are so constant that I feel that they deserve much more study. The gradual decrease in numbers during the growth of a neutrophil leucocytosis suggests:

(1)  That mononuclears are destroyed or redistributed in the same manner as the neutrophils.

(2)  That their regeneration is not so rapid or not so necessary as the neutrophils. This is in agreement with Carnegie Dickson's [11] findings that the bone marrow reactions specialize in particular types of cells though reactions affecting one class to the exclusion of all others is rare.

The increase of mononuclears during the fall of a neutrophil leucocytosis suggests that these cells have some function in connection with reconstruction. They may be scavengers. These are only tentative hypotheses and are not settled opinions. The data are insufficient. In dealing with the neutrophils the observations of others were able to fill up the deficiencies in my own, but this has not been the case with regard to the mononuclears.

Some explanation is necessary in connection with the/

the sudden marked mononuclear increase at the height
of the leucocytosis in Graph II, Table II.    In this
case, as in all the others, I had duplicate films, but
in neither set had I succeeded in getting the granules
well stained.    In other films, from this and other
patients, neutrophil promyelocytes were seen.    They
were few in number and did not affect the percentages
to any material extent.    It is possible that in this
case an unusual increase had occurred and that owing
to the staining the neutrophil premyelocytes could
not be distinguished from lymphocytes.    It is the
only explanation that I can offer.

Cabot[19] has published the records of a few cases
in which lymphocytosis seems to have taken the place
of a neutrophil leucocytosis.    But I do not think
his findings have a bearing on this case, in which the
increase of lymphocytes apparently only existed for
an hour or two.

The variations in the numbers of mononuclears need
more study.

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# SUMMARY.

(1) In certain cases of Rheumatoid Arthritis which were being treated by intravenous peptone injections, total and differential leucocyte counts and Arneth counts were made in series.

(2) These observations showed:-

    (a) An initial Leucopenia, which was succeeded by

    (b) A Neutrophil Leucocytosis, which showed

    (c) A shift to the left in Arneth's Count.

    (d) The Mononuclear leucocytes showed a constant variation in numbers.

(3) Each of these findings has been compared with the published work of other observers.

(4) Arneth's claim that his classification divides the polymorphs in accordance with their ages is discussed and found correct.

(5) The Leucopenia is due to a redistribution or destruction of white blood corpuscles or a combination of the two processes.

(6) The same processes continue throughout the leucocytosis which really commences during the leucopenia. The numbers of leucocytes in the peripheral blood only represent a fraction of the numbers/

numbers which are produced by the bone marrow.
Large numbers of leucocytes are used up in the
process of attaining immunity against the peptone.
These do not appear in the peripheral blood stream
and so are not counted.

(7) Certain practical suggestions are offered as a
result of this.

(8) Comments are offered on the use of Arneth's
classification as an aid to prognosis.

(9) The variations in numbers of the mononuclear cells
has been briefly discussed.

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