THESIS

on

SUDDEN or UNEXPECTED DEATH

with

Special reference to

1. STATUS LYMPHATICUS

and

2. POST-OPERATIVE PULMON-
:ARY EMBOLISM with

records of fifty-five cases, and with the results of experiments on coagulation-time of the blood be-
:fore and after surgical operation.

by

SIDNEY ELISABETH CROSKERY,
B.Sc., M.B., Ch.B.

M. D. 1927

PART I.

S Y N O P S I S .

INTRODUCTION .. Unexplained sudden death - Status Lymphaticus - collective investigation.

METHOD .. Details of examination of cases of sudden death, etc.

NOTES OF CASES

A.I. - Sudden unexpected deaths where a sufficient cause was found at post-mortem (19 cases).

A.II. Cases where no obvious cause of death (7 cases).

A.III. Deaths due to accidents (21 cases)

arranged to illustrate age differences in the thymus.

B. - Cases of death from any cause in persons of 15 years or over who have an apparently glandular thymus (8 cases) - several cases which showed no regeneration of thymus - four cases transferred from A.I., one from A.II and three from A.III.

C. Thymuses from various cases showing:-

C.I. Primary atrophy - marasmus - one case.

C.II. Secondary atrophy - chronic wasting diseases (10 cases).

C.III. Secondary atrophy - acute diseases (11 cases) Encephalitis Lethargica.

COMPARISON Of "Accidental" and age atrophy of the thymus.

DISCUSSION Of the function of the thymus with References to Literature and to the/

"Why does sudden death occur ? No one dies suddenly apart from the effects of violence as long as all the organs are sound."[1] Sudden death is defined by Brouardel[1] as "the rapid and unforeseen termination of an acute or chronic disease, which has, in most cases, developed in a latent manner."

Death, it used to be said, takes place by the heart, the lungs or the brain to which Brouardel[1] adds the kidneys and the "humours."

Pulmonary embolism will be discussed in the second part of this thesis. It is one of the best examples of a rapid and unforeseen death which may be ascribed to disease of circulatory, respiratory or humoral systems.

Brouardel[1], however, as well as other medical jurists, admits that even after the most careful post-mortem examination 8 to 10% of sudden deaths are un-:accountable. Deaths due to strong emotions or following slight injury to or irritation of certain parts of the body, such as the epigastrium during the process of digestion, were held by Brown Séquard[2] to be due to "Inhibition". In these cases death takes place without a struggle, without convulsions, by re-:flex inhibition of the vital functions; just as by irritation of the nasal mucosa a reflex excitation of complex movements results in sneezing[1].

Brouardel[1] /

Brouardel[1] believes that many such cases may be restored to life by artificial means employed immed-:iately because it has been observed that the venous blood remains red for a very long time in these cases. McWilliam[3], however, believed that recovery is pre-:vented in cases of fatal syncope by the cardiac ventricles going into fibrillation.

Brouardel[1] gives as an occasional cause of sudden death "special unfortunate susceptibilities of the individual". It was observed by Plater[4] in 1614 that persons dying suddenly without assign-:able cause were often found to have an enlarged thymus; and the Status Lymphaticus has been a sub-:ject of controversy since it was first defined by Paltauf[5] in 1889 as "the manifestation of a constit-:utional defect of a chlorotic-lymphatic nature which so lowered the resistance that such individuals were unable to withstand unusual shocks and strains".

As a cause for deaths during anæthesia or after slight operative procedures the diagnosis of lymph-:atism was becoming a "refuge for the destitute", (Dudgeon)[6].

A collective investigation[7] on Status Lymphati-:cus was organised by the Medical Research Council in conjunction with the Pathological Society of Great Britain and Ireland. The objects are to investigate all cases of sudden death in apparently healthy persons/

persons of any age from the point of view of status lymphaticus and all cases of death in persons of 15 years or over who have an apparently glandular thymus, and also by measurements of thymus and lymphatic tiss-:ue in accident cases to increase statistics of the normal size of the thymus and its relation to body weight at different ages.

In connection with the Status Lymphaticus In-:vestigation, I have examined (A.) forty-seven cases of sudden death of which twenty-one were caused by accidents, and (B.) eight cases of persistent thymus in adults.

A most remarkable feature of the cases is that eight of the cases of A. would also come under the heading B, and in five of the cases of A. under fif-:teen years of age, excess of lymphoid tissue was noted and the thymus was above the average weight of the age period as given by Bratton[8] in three cases.

The details of the method of examination are as follows:-

The weight and length of the body are measured; also the weights of the heart, both kidneys and the spleen.

The thymus is carefully dissected off, its great-:est length, breadth and thickness measured and its weight./

weight. A note was made as to whether or not any part encircled the trachea. Cross sections were cut through the thickest part for examination microscopi-:cally so that the percentage of glandular to adipose tissue might be gauged. In adults it was usually observed that a bilobed mass of fat replaces the thymus on the anterior surface of the pericardium retaining its shape.

The narrowed upper portions of the two-lobed mass, which run up towards the lower poles of the thyreoid (and were often found to have a parathyreoid attached to the tip) are easily found in almost all cases as two parallel strips of fatty and fibrous tissue - and it was in these portions that remains of glandular tissue were most easily found in adults.

The percentage of gland to fat is of course of much greater importance in adults than the actual weight of the mass which varies with the adiposity of the individual.

It was found in young people, 16-20 years of age, that the involution and fatty replacement of the thymus occurred from below upwards - the large lobes spread out over the pericardium, being invaded before the upper parts, while in cases of regeneration - e.g. hyperthyreoidism - the lymphoid tissue could be seen growing down into the fatty mass in the reverse direct-:ion./

direction.

In several cases a wet film, fixed in mercuric chloride, was taken from the softened inner parts of the glands in young people. This pus-like fluid was found, as described by Dudgeon[6], to contain no in-:flammatory cells, merely lymphocytes, red blood corpuscles, a few endothelial cells and eosinophils.

The microscopic sections were all done by the paraffin method, after fixing in 10% formalin, and were stained Hæmatoxylin and Eosin, and Eosin and methylene-blue - a few frozen sections were cut to demonstrate the proportions of fat to glandular tissue.

Further measurements were made of the lymphoid tissue in different parts of the body - the largest gland found in each area being measured - faucial and lingual tonsils, cervical coeliac and mesenteric glands, Peyer's patches and solitary follicles of small and large intestines and follicles of cardiac and pyloric regions of the stomach if these were ob-:vious. In all cases also a note was made as to the amount of lymphoid tissue present in these areas, whether normal, sub-normal or excessive. Lastly, the Malpighian bodies in the spleen were measured under the microscope, the average of the five largest bodies seen on two or more large sections of spleen stained hæmatoxylin only, the smaller diameter of the oval bodies of course being taken.

On the Record Cards the following details are also asked for: State of nutrition and evidence of feminism in males, cause of death and major pathological conditions, and any other observations - such as, for instance, congenital abnormalities and pathological lesions of less importance.

In cases in which the cause of death was not obvious at the post-mortem, certain other investigations were to be made.

Microscopic sections of muscle of left ventricle were examined for fat; of lung, for capillary bronchitis, etc., of suprarenals and parathyreoids, of mid-brain, medulla and cord, of kidney, liver and spleen, of the bones for rickets, and a blood culture for septicaemia was obtained if possible, but often the heart and cerebral sinuses had been opened in the search for a cause of death before it was discovered that this was "not obvious".

In my series of cases the above microscopic examinations were made in almost every case whether the cause of death were found or not, and in addition, a frozen section of lung was examined for fat capillary embolism e.g. in accident cases; and sections of the thyreoid and sometimes the pituitary glands were examined and a piece of voluntary muscle from the diaphragm and in a few cases the coeliac sympathetic garglion. In all cases of enlargement of lymph/

lymph glands they were examined microscopically for tubercle unless this was obvious naked eye.

Twelve of the cases were incomplete and were sent in as brief records where only measurements and weight of the thymus were obtained and sections of it with notes of post-mortem findings, excess of lymph-:oid tissue and with or without a note of the weight of the body.

In three cases at the beginning of the research no measurements but only micro-sections of all the tissues including the thymus were made.

Besides these cases for the Medical Research Council Investigation, a series of twenty-four thymus glands, C, from all sorts of cases were examined.

These were mostly from children dying of acute or chronic disease at the Royal Hospital for Sick Children obtained through the kindness of Dr. Agnes Macgregor - two from premature fœtuses from Dr. Gladys Dodds.

The following are notes of cases examined under heading A which I have subdivided into three classes -

I. Cases of sudden or unexpected death where a sufficient cause was found at the post-mortem.

II. Cases of sudden death where no sufficient cause was found.

III. Cases of accidental deaths.

Brief/

Brief notes of cases of A.I. follow:-

Case III.- male aged 60, suddenly collapsed and died in ten minutes, had had frequent haemorrhages from a papilloma of the bladder.

Post-mortem.- fatty infiltration of heart, oedema of lungs.

Case VIII.- male aged 57, fell unconscious while at work and died in a few minutes - three hours before had complained of indigestion.

Post-mortem.- chronic interstitial myocarditis, dilatation of left ventricle, marked œdema of lungs, oedema of brain.

Case X. - female aged 68, sudden collapse when up for the first time thirteen days after an accident - Pott's fracture - died in a few minutes without dyspnœa, cyanosis or pain in the chest.

Post-mortem.- very fat, fatty infiltration of heart, marked congestion of both lungs - no ante-mortem clot in veins.

Case XI.- male aged 54, took ill suddenly, cyanosis, dyspnœa, unconsciousness and died in 40 minutes.

Post-mortem.- Hæmorrhage into a glioma of right cerebral hemisphere, specific arteritis.

Case XII.- male aged 69, found unconscious died within 24 hours - heavy drinker.

Post-mortem.- Œdema and congestion of brain and oedema of lungs, hydroureter with atrophy of left kidney, right cystic, uræmia.

Case/

Case XVIII. - male aged 51, admitted as acute abdomen, coughed up copious watery frothy sputum, died in three hours.

Post-mortem.- Marked pulmonary oedema and pleur-:al effusion, fatty change in myocardium.

Case XX.- female aged 10 years, "laryngismus stridulus", tracheotomy, unexpected death.

Post-mortem.- Diphtheritic membrane in pharynx film showed bacilli with metachromatic granules - no growth of B. diphtheriæ on culture, pulmonary œdema and capillary bronchitis. Thymus is described later under C.III.

Case XXII.- female aged 63, under treatment in R. I. E. for rheumatoid arthritis, died unexpectedly 16 hours after onset of abdominal pain and vomiting.

Post-mortem.- Peritonitis from small perforation of a carcinoma of the pelvic colon. This case was taken also because great excess of lymphoid tissue of tongue and intestinal follicles raised the suspicion of "B".

Thymus weight 5 grams 7% lymphoid.

Case XXIII.- male aged 59, found dead in bed by nurse a few hours after admission to hospital, history of post encephalitic Parkinsonism and two attacks of angina pectoris.

Post-mortem.- Atheroma of coronaries, fatty de-:generation of muscle of left ventricle. Great excess of/

of lymph follicles in intestines - spleen weight 220 grams but no excess of lymphoid tissue. Thymus weight 3½ grams - 0·25% lymphoid.

Case XXX.- Male aged 24, died 24 hours after operat-:ion for tonsils and adenoids.

Post-mortem.- Large abscess in right temporal lobe of brain and purulent exudate at base of brain - chronic otitis media. This case will be described further under B.

Case XXXI.- Female aged 58, sent in as acute obstruct-:ion or acute encephalitis - unconscious for two days before death.

Post-mortem.- Caseous mass of tuberculous glands in mediastinum, miliary tubercles in organs.

Case XXXIII.- Male aged 58, admitted in coma, died next day, history of encephalitis lethargica in April 1926.

Post-mortem.- Subdural haemorrhage and haemorr-:hage in centre of mid-brain, apoplectic cyst in corpus striatum. Excess of lymphoid tissue in pharynx and mesentery, spleen weight 230 grams but not excessively lymphoid; adenomatous cyst in thyreoid . Accessory cortical (interrenal) body in neck. Thymus weight 10 grams, 7% glandular.

Case XXXVI. - Female aged 25, died suddenly with "air hunger" after recovery from ether anaestesia for forceps delivery of living child. She had had chloroform/

chloroform eight days before for induction and ether during a second attempt at induction some days later.

Post-mortem.- Early broncho-pneumonia, cloudy swelling and fatty change in liver and kidneys, no sepsis or haemorrhage in genital tract which was norm-:al for her condition. Necrosis and hæmorrhage in suprarenal.

This case will be described under B.

Case XXXVII. - Male aged 15, died 12 hours after operat-:ion, under intra tracheal ether following chloroform induction for removal of fibro-sarcoma of maxilla, internal cerotid was tied. He had had an anæsthetic some months previously for introduction of radium.

Post-mortem.- Heart flabby and dilated, early diffuse fatty degeneration, cloudy swelling and marked fatty change in liver and toxic kidney, lung early stage of inhalation pneumonia, altered blood in stom-:ach.

This case will be further studied under B.

"L" - male aged $2\frac{10}{12}$, sudden death after operation to drain elbow joint for pneumococcal arthritis.

Post-mortem.- Diphtheria.

This case will be described under C.III.

"Q" - male aged 40, found moribund in public house.

Post-mortem.- Lobar pneumonia. Thymus 2 grams 1% glandular.

"M" - Male aged 30, sudden death.

Post-mortem.-/

Post-mortem.- Pontine haemorrhage, chronic interstitial nephritis.

See under B. also.

"AA" - male aged 41 years, died under chloroform, oper-:ation for tumour of maxilla.

Post-mortem.- Heart large and flabby - a nodule in septum proved to be a gumma as did the tumour in the maxilla.

Well-developed, well-nourished, 6 ft., 11 st. 6 lbs. Thymus weight 10 grams only 10% glandular. Hassall's corpuscles numerous, no eosinophils seen.

"AN"- female aged 3½, acute obstruction after tonsill-:ectomy operation.

Post-mortem.- Tuberculous mass blocking intestine, fairly well-developed, 3 ft. 3 in., 2 st. 12 lbs.

Thymus weight 9·8 grams.

It will be noted that many of the common causes of sudden and unexpected death are represented in this series, and that they occurred mostly in elderly peop-:le or children. Four cases, all young adults are to be described under B.

In order to save repetition, I give here a list of the various types of Hassall's corpuscles seen in thymus glands so that I may refer to them by the numb-:ers in the descriptions which follow:-

1./

1. Cellular type - young and composed of two or three enlarged epithelial cells - no concent-:ric arrangement.

2. Concentric - the centre is bright pink - stained with eosin, degenerated material ? hyaline, surrounded by one or more rings of flattened epithelial cells.

3. Concentric type with infiltration by cells polymorph neutrophils, and occasionally eosin-:ophil leucocytes.

4. Concentric type with masses of dots of vari-:ous sizes usually basophil in the clear central part.

5. Concentric type with fatty degeneration shown by clear space round nucleus.

6. Concentric type a little larger and showing calcification in the centre.

7. Compound corpuscles, several cellular and concentric types massed together.

8. Flaky type larger than concentric, oval or round masses of paler pink flakes lying loosely or closely inside a narrow capsule formed of flattened cells. Cooper[9] Intermediate stages between 2 and 3 and 8 are often found.

9. Flaky with some of the flakes calcified.

10. Enormous flaky corpuscles often visible to the naked eye.

11. Compound flaky and cellular or concentric.

12. Completely calcified often no layer of flattened cells round them.

13./

13. Spaces probably were occupied by flaky or calcified types often no layer of flattened cells.

14. Cysts of great size lined by several layers of flattened cells and with some pale-pink granular material in them.

Cases of A II, sudden deaths where no sufficient cause was found:

Case I. Female aged 50, death during anaesthesia with C_2E_3 mixture, on the introduction of the cysto-:scope - history of breathlessness and palpitation on exertion, and of two previous abdominal operations, not emotional.

Post-mortem.- Large birth-mark on face, poorly developed and thin, 4 ft.9½ in. , 6 st. 5¼ lbs. evid-:ence of rickets.

Heart rather flabby, brown atrophy, chronic gast-:ric ulcer, no haemorrhage, old healed pyelonephritis, slight excess of cerebro-spinal fluid, brain more diffluent than usual, nil abnormal microscopically, lung congested, some collapse: Suprarenal and thyreoid normal; slight excess of lymphoid tissue on tongue pyloris and ileum and large Malpighian bodies in spleen, with obvious germ centres. Thymus not weighed - 3% glandular; vascular masses in fat with thick-walled vessels, reticulum cells and few lymphocytes. Few Hassall's/

Hassall's corpuscles of the types 3 and 12, no eosin-:ophils seen, tissue next cells present.

Cause of death probably cardiac failure.

Case II. Female about 50, death during induction with C_2E_3 after ℥ iij of the mixture (two drachms) gynecological operation.

Post-mortem.- Poorly developed and poorly nourished, no rickets, inflammatory mass in pelvis matting organs together, pus in left tube, chronic inter-:stitial nephritis, hypertrophy of heart and some fatty infiltration, lung nil abnormal; liver capill-:ary congestion cloudy and fatty change; cause of death probably heart failure due to hyperthyreoidism.

Described further under B.

Case XVII. Female aged 36, sudden death eight days after operation supravaginal hysterectomy for fibroids, history of menorrhagia and debility for a year. Suddenly became unconscious with conjugate deviation to the right, slight cyanosis, no dyspnœa, heart dilated and œdema at both bases.

Post-mortem.- Heart slight fatty infiltration and dilatation, no sign of pulmonary embolism: heal-:ing wound, no sign of peritonitis: liver cloudy swelling: kidney narrowing of cortex, congestion: slight increase in cerebro-spinal fluid, congestion of surface of brain, no meningitis: on section, the only lesions found were greyish patches in both optic thalami/

thalami, caudate and lentiform nuclei. Microscopi-:cally no abnormality was found except a mass of epen-:dymal cells lying near the central canal in upper part of cervical cord.

Thyreoid not enlarged, increase of interlobular fibrous tissue, two nodules of lymphoid and endothel-:ial cells, possibly thymus but no Hassall's bodies; vesicles various in size well filled with colloid, stained pale-pink with eosin.

Suprarenal "chrome cells" well-marked; para-:thyreoid nil abnormal, both basophils and eosinophils seen in stroma.

Average development and nutrition, 5ft. 7in., 9st. 4lbs., no sign of rickets.

Some lymphoid excess in the spleen and in lingual, cœliac and mesentric regions (some tubercle in glands) Blood in vessels in all the organs seems to contain excess of lymphocytes of large and small types; thymus 12·9 × 2·9 × 1·2 cms. weight 11·5 grams, 45% glandular in fat with well-formed fibrous strands and thick-walled vessels, mostly medulla with patches of cortex here and there: Hassall's corpuscles numerous mostly 1, 2 and 7; also 3, 5 and one 13.

Eosinophils seen had large pale central nuclei. Basophil tissue mast cells were also seen in the stroma.

Case XXI. Male aged 5 years, sudden death five minutes after recovery from anaethesia after operation for/

for removal of tonsils and adenoids, pale not cyanosed, tracheotomy and artificial respiration tried with no effect.

Post-mortem.- Well-developed, very well-nourish-:ed; 3ft. 7in., 3st. 11 lbs.; pale, waxy skin, no feminism, no rickets.

No obstruction in air passages, lung microscopic some congestion and collapse, some fluid in alveoli and catarrhal cells containing brown pigment, bronchi walls congested contain desquamated cells, red-blood corpuscles, polymorphs and catarrhal cells in fluid. Heart normal, 87 grams, very slight atheroma in sin-:uses of Valsalva: kidney, slight pin-point haemorr-:hages in pelvic mucosa.

Thyreoid divided into lobules by fibrous tissue, very vascular, vesicles of varying size and shape contain pale-stained colloid lining cells cubical or columnar, "piling" of cells and cells lying free on the colloid are frequent, large round clear spaces in colloid. This is the normal appearance in child-:hood,(Cooper[9]).

Suprarenal, cortex rather narrow, probably normal at this age; zona fasciculata well filled with lipoid, great general lymphoid enlargement of tonsils (removed at operation with adenoids) lingual tonsil and folli-:cles of intestine. Seven large Peyer's Patches along with numerous aggregated follicles occurred in the lower two feet of ileum. Cervical, coeliac and mesentric/

mesentric glands were greatly enlarged; there was some tubercle in the mesenteric; spleen 115 grams, Malpighian bodies large and numerous ·063 cm. in diameter; spleniculus. Masses of lymphocytes appear-:ed in walls of bronchi and in portal tracts of liver, with many polymorph eosinophils. Eosinophils were numerous in lymph glands, spleen and spleniculus.

Thymus 8·9 × 5·9 × 1·1 cms. weight 26 grams 100% glandular, medulla more obvious than cortex, lymphocytes adhere in clumps of three or four. Hassall's corpuscles many 1, 2 and 7, also 3, 5, 6, 8 and 9 and one 10.

Eosinophils numerous especially with large pale single nucleus, or smaller dark and eccentric, few polymorphs. Basophil tissue mast cells are numerous in the stroma.

The slight bronchitis present seems insufficient to cause death which appears to have been due to syn-:cope rather than to respiratory failure.

The thymus in this case seems to be definitely above standard weights. Bratton[8] gives 23·21 grams average for boys 5 - 6 years; Hammar[16] 22·98 grams; Schridde 15 - 17 grams; Ronconi 16·75 grams; Klose 15 grams; London Hospital 24·19 grams for ages 1 - 5 years and under 6 years. Friedleben[10], however, gives 3 - 14 years average 26·31 grams.

Case XXV. - Male aged 14, unexpected death in ward while/

while under treatment for post-encephalitic Parkinson-:ism: Previous appendectomy.

Post-mortem.- Fairly well developed but thin, 5 ft. 8 in., 8 st. No feminism, no rickets, lung general congestion, small areas of consolidation round bronchioles with red blood corpuscles, catarrhal cells and polymorphs, many of the latter being eosinophils; pleural cavities, a little free fluid in each.

Heart, 200 grams, slight dilatation of right ventricle, bicuspid aortic valve, a little atheroma in sinuses and at mouths of branches in abdominal aorta. Diameter of aorta above valve 4·7 cms.

Liver and kidney congestion and cloudy swelling. Foetal lobulation of kidneys marked. Brain congest-:ed, oedema of pia-arachroid. Thyreoid normal for his age, irregularity in size and shape of vesicles which contain pale-pink staining colloid, cubical lining cells often doubled and "piled". Lobulation well marked, eosinophils in interlobular stroma.

Suprarenals, weight of both together 9·5 grams, both show little yellow nodules of cortical tissue outside the capsule; congested one small area of haemorrhage in cortex. Chrome cells are present in clumps.

General lymphoid enlargement especially in pharynx, stomach, cardiac and pyloric regions and intestines, also cervical, coeliac and mesenteric glands, but act-:ive /

active tuberculosis is present in neck and mesentery. Spleen weight 165 grams, excessive numbers and size of Malpighian bodies, 0·045 cm. diameter. Masses of lymphocytes in portal tracts with many eosinophils both mono- and polymorphs. Eosinophils also numerous in lingual tonsil.

Thymus 16 × 8·8 × 0·75 cms. weight 39·4 grams, 97% glandular, bands of pale-pink œdematous looking fibrous tissue separate lobules: vessels fairly thick-walled: medulla and cortex well demarcated.

Hassall's corpuscles many 1, 2, 3, 7 - also 8 and 9. Eosinophils numerous singly or in clumps, mono- and polymorphonuclear.

The thymus of this case also is larger than most of the standards; Bratton[8] gives 26·71 grams for males 14 - 15 years: Hammar[16] 10 - 15 years 37·52 grams. Schridde 25 grams, Ronconi 28·25 grams, Klose 25 grams, London Hospital 27·24 grams.

Early broncho-pneumonia was discovered micro-:scopically but apparently there were no signs or symptoms of this before death. He succumbed very quickly to an acute infection.

"G" - a child aged $\frac{2}{12}$, found dead in bed - nothing pathological except a large thymus which was sent un-:fixed from the country.

Thymus weight after formol fixation 31 grams 100% glandular; the medullary portions of most of the lobules had softened and fallen out so that not many Hassall's /

Hassall's corpuscles were seen. These were of types 1, 2, 7 and 8. Eosinophils not excessive.

The weight of the thymus is above all the standards - Bratton[8] gives 19·06 grams as average weight for ages 2 days to 3 months.

"O" male aged $\frac{4}{12}$, sudden death twelve hours after hernia operation; temperature rose suddenly to 105° .

Post-mortem.- Toxic appearance of kidneys. Thymus 15 grams, general lymphoid enlargement.

Thymus 100% glandular, cortex and medulla well-demarcated, Hassall's corpuscles not excessive in numbers, mostly 2 and 7, 1, 3 and 8 also seen. Eosin-:ophils not increased.

The thymus is smaller than Bratton's standard 25·83 grams for males of 3 - 6 months.

Of these seven cases of sudden death from in-:sufficient causes, one is a case of "B"; three cases showed a thymus above the weight standards, and two of these - Cases XXI and "G" are typical "thymus deaths". Case XVII also showed a large percentage of glandular thymus for an adult. Three of the cases are anæsthet-:ic deaths, another occurred twelve hours and another eight days after operations.

A.III.- Under this heading are twenty-one cases of deaths from accidents, and three neonatal cases. All these cases died within a few hours of the accident, under twenty-four hours at latest, and it may be taken that in every case trauma was so severe as to be a sufficient cause of death - so that only lesions not attributable to the accident will be mentioned.

In order to illustrate age differences in the thymus, the cases are arranged in order of age and the weights of the thymus given for each case. For comparison, I have put in brackets after each the average weight of the thymus for that age and sex as given by Bratton[8] or Friedleben[10].

Histological descriptions are given of one gland from each age period as a type.

Premature fœtus

"S" male, six months, still-born, cause of death prematurity. Thymus 0·5 grams (2·3 grams - Friedleben[10]) 100% glandular, cortex and medulla well demarcated, medulla small, Hassall's corpuscles not numerous, types 1, 2 and 7; a few 4 and 5. Numerous eosinophils mono- and polymorph.

"R" male, 7¼ months, lived eight hours, cause of death, cerebral haemorrhage. Thymus 2 grams (2·3 Friedleben) 100% glandular, cortex well demarcated from/

from and much wider than medulla. Hæmorrhage into centre of some lobules. Hassall's corpuscles not numerous, types 1, 2 and 7. Numerous eosinophils.

Full-time child

"AJ" - male aged 2 days, full-time, well-nourished, cause of death malaena neonatorum duration 9 hours from bleeding polypus in duodenum. Thymus 11 grams (11·77 Bratton[8]) 100% glandular, cortex and medulla well demarcated, equal in width, Hassall's corpuscles numerous 1, 2, 7; also 3, 4 and 5. Enormous numbers of eosinophils in groups in septa and with blood vessels - many have large pale central nucleus but small dark mono- and polymorphs are also numerous. One or two basophils tissue - mast cells were seen in the stroma, one with a bilobed nucleus. (Cooper[9]) considers that mast cells appear only in aging glands and those showing accidental involution, but I have found them in thymus at all ages.

Childhood

Case VI - Male aged 3, well-developed and nourished, 3 ft. 2½ in., 2 st. 10 lbs. Thymus 24·25 grams. (28·24) slight general excess of lymphoid. Large Meckel's diverticulum.

Case XXXIX - Male aged 3½, well-developed, 3 ft. 7 in. 3 st. 2 lbs. Thymus 22 grams (28·24) 100% glandular, thin-walled vessels, cortex and medulla well demarcated and/

and cortex wider, Hassall's corpuscles numerous - 1, 2, 3, 4, 5 and 7, 8, 9, 10, 11. Eosinophils very numerous mostly pale mono-nuclears. A few large mast cells seen in stroma.

Case XXVI- Female aged 6, well-developed and nourished, tubercle in neck and mesentry, hydroureter with atrophy of left kidney. Thymus 24 grams (20·67) 99%

"AE"- Female aged 7, well-developed, organs healthy. Thymus, medulla and cortex well demarcated, about equal width, thin walled vessels in stroma, Hassall's corpuscles numerous, mostly types 1, 2, 3 and 7 also 5; also 8, 9, 10 and 11 in Case XXVI. Eosinophils very numerous, many pale mononuclears. Numerous basophil tissue mast cells.

Case XVI - Male aged 8, was run over immediately after leaving the Infirmary where he had been treated for five weeks following a previous run-over accident - fracture of humerus: well-developed and nourished, 4 ft. 4 in., 5 st. Suprarenals small, cortex narrow, thyreoid, irregularity of vesicles, some active, some large and full of colloid with space in it. Para-thyreoid fatty infiltration divides the gland into pseudo acinar formation - this appearance should only occur in adults Pool[11]. Excess of lymphoid tissue in mesentery, spleen 125 grams and spleniculus. Thymus 38·3 grams (23·55) 100% glandular, cortex not well de-:marcated, mostly medulla. Hassall's corpuscles many

1 /

1, 2, 7; also 8 and 9. Many eosinophils with small round eccentric dark nucleus and polymorphs.

Case VII. - Male aged 10, well developed, thin, 4 ft. 3½ in., 3 st., persistent thyreo-glossal duct, slight atheroma of aorta suprarenal cortex rather narrow - well filled with lipoid.

Lymphoid tissue moderate excess on tongue and mesentery.

Thymus 25·3 grams (31·8) 95% glandular.

Case XLI. - Female aged 10, well developed, 3 ft. 8 in. 4 st. 4½ lbs., strand of thyreoid tissue stretching from isthmus to hyoid bone. Some lymphoid excess in neck and mesentery, not tubercle, and spleen large follicles.

Thymus 20·3 grams (26·8) 100% glandular, vessels rather thick-walled, cortex and medulla well demarcated equal in width, Hassall's corpuscles not very numerous, types 1, 2, 3 and 7. In case VII, also 8 and 9. Eosinophils numerous mono- and polymorphs.

Puberty

"AD" - Male aged 15, well developed, 4 ft. 10 in., 8 st. 4 lbs. - pus in pelvis of one kidney. Thymus 12 grams (25·92) 85% glandular. Well-formed old fibrous strands and fatty tissue replacement, some cellular fibrous tissue also. Medulla exceeds cortex in width, numerous Hassall's corpuscles, many 3, also 1, 2, 4, 5, 7, 8 and 9. Many eosinophils.

Case XLV/

Case XLV. Male aged 17 - Thymus 47·5 grams (25·92 at 15 - 16 years) to be described under B.

Young Adults

Case XLIII. Male aged 21, very well developed, 6 ft. 12 st. 4 lbs., no sign of feminism, small thin aorta, heart 370 grams.

Thymus 11 grams, 75% glandular.

Case XLIV. Male aged 22, moderate development, muscu-:lar, 5 ft. 9 in., 9 st. 11 lbs. Internal cerebral hæmorrhage, sub-endocardial haemorrhage, colloid goître. Thyreoid weight 50 grams, strand of tissue runs up to hyoid. Small aorta, heart weight 270 grams, excessive lymphoid tissue in mesentery and spleen 190 grams.

Thymus 1 gram, 75% glandular.

Case XV. Male aged 23, well developed, 5 ft. 8 in., 11 st. 6 lbs., heart 340 grams, aorta normal.

Thymus 12·3 grams, 75% glandular. Patches of thymus tissue being infiltrated by fat, very thick walled vessels in stroma, less thymus and more fat in lower cuts across the gland. Patches are mostly medulla with round or oval masses of lymphocytes re-:presenting the cortex lying at the side, and some even embedded in the medulla giving the appearance of "glande invertée". Hassall's corpuscles fairly num-:erous, mostly 10; also 8, 9, 11, 12, some 1, 2, 3, 4 and 7. In case XLIV. - no 8 etc. but 13. Fairly numerous eosinophils scattered and in bunches, many tissue/

tissue mast cells in stroma and also seen invading the thymus masses.

Adults

Case IV. Female aged 30, alcoholic, ? suicide. Thymus 17·95 grams, 60% glandular - See further under "B".

"P" Male aged 38, well developed, 6 ft., 12 st. - haemorrhage in right suprarenal due to violence prob-:ably. Thymus 9·6 grams, 15% glandular.

Case XIX. Female aged 55, suicidal fall from window; Thymus 6·4 grams, 35% glandular - See further under "B".

Case XIV. Male aged 61, 5 ft. 9 in., 11 st. 6 lbs., slight chronic interstitial nephritis, dilated left ventricle, weight 405 grams. Thymus 0·4 grams, 7% glandular.

Case XXIX. Female aged 65, 5 ft. 3 in., 9 st. 2 lbs., thyreoid mass of lymphocytes and fibrous tissue vesi-:cles irregular in size, some immense - others small pale colloid, peculiar granules staining some with basic, some with acid dyes in free part of columnar epithelial cells next the lumen - perhaps an early Riedle's struma. Parathyreoid shows many small vesi-:cles, secretion staining purple with eosin, methylene-blue and pink with methyl-violet.

Spleen showed small curled up masses of hyaline material in Malpighian bodies - negative to amyloid stains/

stains - faint outlines of red blood corpuscles seen in them. Cardiac hypertrophy, weight 420 grams. Thymus 10·5 grams, 1% glandular. Thymus in middle age similar to adult but thinner strands of tissue in fat, surrounded each mass by reticulum cells, a few lymphocytes found in centre, very few Hassall's corp-:uscles mostly 12 or 13 or 14; in Case XIV, types 1 and 2 were quite numerous. Case XXIX, showed prolif-:eration of the intima of the thymic arteries, almost obliterating the lumen with calcified patches at inter-:vals in the media.

No eosinophils seen - basophils occur in stroma.

Old Age

"U" Male aged 70, 5 ft. 8 in., 11 st.; parathyreoid adherent to tip of thymus showed fatty infiltration not very advanced, great vascularity, some basophils, no eosinophil leucocytes seen, no vesicles. Thymus 1·2 grams, 3% glandular. Small rounded and elongated mass in fat vascular at edges, composed of elongated cells and a few lymphocytes and reticulum cells. Hassall's corpuscles, a few of types 1, 2 and 5 seen, no large ones. No eosinophils, numerous basophils near vessels.

It will be noted that three out of this series of "normal controls" have had to be transferred to heading "B"; possibly the three young adults would also have been examined under "B" for their 75% thymuses and certain/

certain stigmata of lymphatism.

Of the children, three are well above the average weight of thymus for their age and sex while others are markedly below the average without showing any histological evidences of accidental involution. En-:larged lymph glands were present in nine cases and enlarged follicles in intestine in six.

The heart or aorta was small in three cases; early atheroma was present in two of the children; sub-endocardial hæmorrhage, without body injuries, occurr-:ed in three cases. Foetal abnormalities were pres-:ent in five cases.

B. Cases of death from any cause in persons of 15 years or over who have an apparently glandular thymus. Some cases were taken, although the thymus did not look completely glandular, because other lymph-:oid enlargement was found or some of the stigmata of Status Lymphaticus were present.

Case V. Male aged 50, Wassermann +++, "white pneumonia" and oedema of lungs and purulent bronchitis (tubercul-:ous), myocardial hypertrophy, specific arteritis, sclerosed kidney, etc.

Normal development, 5 ft. 7 in., no feminism, no rickets. Lymph follicles of intestine obvious, haemo-lymph glands enlarged in abdomen, few germ centres in these, many large mononuclears containing brown pigment. Spleen very large, 250 grams, and spleniculus which has a/

a structure like fatty bone marrow.

Suprarenals large, well marked chrome cells. Thymus 3·4 grams 50%, no demarcation of cortex, lymph-:ocytes numerous throughout, Hassall's corpuscles types 1, 8 and 12. No eosinophils seen.

Case XXIV. Female aged 60, persistent vomiting for four weeks, no obstruction found at operation - supp-:osed "psychical" .

Post-mortem.- Well-developed, thin, 5 ft. 9 in., 8 st. 4 lbs. Duodenum dilated, ileum congested in patches, sub-acute inflammation without ulceration, no typhoid etc. in intestine or bile.

Heart, flabby chronic myocarditis, brown atrophy, early atheroma of aorta and coronaries.

Kidney, sclerosed, liver, fatty, lung, emphysema and catarrh. Brain and cord, nil abnormal. Thyreoid vesicles mostly small, lined by cubical cells with clear spaces in colloid opposite, many intervesicular cells with small vesicles. Parathyreoid, many fat spaces, basophils seen. Suprarenal, cortex not so much lipoid as usual and in patches, much chrome pig-:ment, medulla congested. Pituitary, very large colloid vesicles in intermediate part.

Lymphoid excess in intestine and mesentery. A lymph gland in the neck showed many eosinophils. Spleen 120 grams: Thymus 4·7 grams, 20% glandular, well-formed fibrous tissue and thick-walled vessels, some/

some fatty invasion of thymic masses.

Hassall's corpuscles numerous - 1, 2, 3, 7 and 8. A few eosinophils - mostly polymorphs seen.

The presence of even 20% of active thymic tissue is remarkable at her age and after a prolonged period of starvation. The thyreoid also shows activity.

Case XXVII.- Female aged 48, had a history of swelling in the neck and dysphagia and tremors for five months, no exophthalmos. Died rather suddenly with rise of temperature to 107°: commencing broncho-pneumonia.

Post-mortem.- Well-developed, fairly nourished 5 ft. 8 in., 10 st., 6 lbs., heart, hypertrophied, 340 grams, marked brown atrophy granules. Liver, advanced fatty change: kidney, marked cloudy swelling: fib-:roids of uterus, one showing degenerative changes. Thyreoid, general enlargement, firm not hard, weight 93 grams. Lobulation well marked, some vesicles large irregular and contain colloid, high columnar lining cells with "piling". In most parts no colloid, very irregular vesicles with infolded walls, columnar, cubical, or syncytial cells coming off the edges. Large clumps of lymphocytes in stroma.

Suprarenal small and thin 5·5 grams and 2·8 grams, narrow cortex, irregular columns in zona fasciculata, very little lipoid in the cells. Chrome cells marked.

General great excess of lymphoid tissue, tonsils large but septic, spleen 290 grams, great many large Malpighian/

Malpighian bodies. Thymus 26·9 grams 98% glandular, thick-walled arteries in the thin fibrous strands, medulla and cortex both present equal in width and well demarcated. Hassall's corpuscles very numerous, a few 8 and 11, mostly 1, 2, 7, 3 and 4. Great numbers of eosinophils in groups along septa and vess-:els, mostly mononuclears but some polymorphs. Baso-:phil tissue mast cells present.

Except for the thick-walled vessels, this thymus is exactly like that of Case XXVI. aged 6. Notice that not only the cortex but the medulla is regenerat-:ed.

Case XXXV.- Female aged 18, died four days after fracture of skull after operation of decompression.

Post-mortem.- Well-developed, very well nourish-:ed, 5 ft. 7 in., 12 st. 2 lbs., capillary congestion of lungs, liver and kidney.

Thyreoid large irregular vesicles full of colloid. Parathyreoid capillaries congested.

Suprarenal, not so much lipoid in zona fasciculata as normal at this age.

General enlargement of lymph follicles and glands, especially in stomach and intestine, spleen 180 grams, large Malpighian bodies.

Thymus 11·5 grams, 11×4×0·9 cms. 60% glandular. Fat and fibrous invasion of masses. Medulla and cortex both present. Hassall's corpuscles numerous, many/

many 1, 2 and 3, some 6 and 8. Eosinophils numerous.

Probably this is a quite normal age involution slightly accelerated by four days inanition.

Case XL.- Female aged 54, toxic adenoma of thyreoid, chronic rheumatism and erythema nodosum, brown pig-:mentation of abdomen and knees. Blood pressure 94/65, failing strength and loss of appetite for a few weeks, acetonurea.

Post-mortem.- Well developed, spare, 5 ft. 8 in., 9 st. 8 lbs., chronic endocarditis of mitral valve, kidney, narrow cortex sclerosed glomeruli.

Liver, marked cloudy swelling, bile pigment in cells, accumulation of cells in portal tracts, mostly lymphocytes with many eosinophils. Thyreoid not en-:larged, pale and homogeneous appearance to naked-eye, divided into lobules by well marked fibrous tissue; only a few vesicles contain colloid, mostly small and empty with infolded walls and great irregularity of lining cells, large oval nuclei and ragged cytoplasm lying free in lumen. Some are lined by a regular row of cubical cells. Large masses of lymphocytes be-:tween vesicles here and there resemble germ centres: Parathyreoid not found: Suprarenal said to be normal to naked-eye - unfortunately not obtained: Coeliac ganglion marked fibrosis separating nerve cells widely. General excess of lymphoid tissue in pharynx and abdom-:en, particularly of para-aortic glands: no tubercle found/

found. Spleen very large and soft, 300 grams, large Malpighian bodies with obvious germ centres. Thymus 5·5 grams, 50% glandular, old fibrous tissue and thick-walled vessels, masses mostly composed of medulla with rounded areas of cortex lying beside them extremely vascular especially round the edges. Hassall's corpuscles few in number, types 1, 2, 4 and a few small 8. Eosinophils fairly numerous. Tissue mast cells large and numerous.

A suspicion of Addison's Disease was raised by the history and appearance of the patient; however, the condition of the thyreoid was quite sufficient to explain the regeneration of the thymus.

Case XLVI - Female aged 60, toxic adenoma of thyreoid, symptoms of weakness, nervousness and tachycardia for sixteen months, developed delusional insanity.

Post-mortem.- 5 ft. 3 in., 9 st., fair develop-:ment and nutrition, heart large and soft with fatty infiltration of both ventricle walls, atheroma of coronaries and descending aorta: Commencing hypo-:static pneumonia in lungs: narrowing of cortex and granularity of kidney with patchy congestion and cloudy swelling: fatty change advanced in liver: slight œdema of brain. Thyreoid, weight 43 grams, uniform-:ly enlarged lobulation marked, some increase in lymph-:ocytes, vesicles very irregular in outline and size; only two or three contain colloid and are lined by high/

high columnar cells: most vesicles empty with irregu-:lar walls, many rows of cells piling and cells coming off into the lumen. Suprarenal, weight of both to-:gether 10 grams, very little lipoid in cortex, very many chrome cells in wide zona reticulata.

Slight increase in lymphoid tissue in intestine and in coeliac glands, spleen 150 grams. Thymus, weight 23 grams, 20% glandular throughout the fatty mass. Thick-walled vessels in the fat, masses not differentiated into cortex and medulla very vascular, vessels dilated, many lymphocytes. Hassall's corpus-:cles many 1, 2 and 7; also 3, 4 and 5 - No large older ones seen. Many eosinophils mononuclear and polymorphs. Many tissue mast cells.

"J" - Male aged 25, acute lymphatic leucæmia.

Post-mortem.- Thymus 23·5 grams, 90% glandular, fat and thick-walled vessels: no differentiation into medulla and cortex, few reticulum cells seen, mass of large and small lymphocytes appears to be invading the fatty tissue: few Hassall's corpuscles, mostly types 10 and 12, some 1, and 7. Eosinophils numerous, mostly polymorphs.

"M" - Male aged 30 (from A.I) Chronic interstitial nephritis and pontine haemorrhage. Thymus section only from upper part, 80% glandular, very thick-walled vessels, fatty invasion of thymic masses which are composed of medulla with masses of cortex lying apart. Large/

Large reticulum cells surround lymphocyte masses. Hassall's corpuscles mostly 10, some 11, some 1, 5 and 7. No eosinophils seen.

"AG" - Female aged 27, peritonitis from ruptured appendix, mentally defective, very fat, 5 ft. 6 in., 10 st. 1 lb., large breasts with an accessory nipple, pubic hair has male distribution, brain and skull no obvious abnormality, uterus small, left ventricle cavity very small, lungs both show four lobes incom-:pletely divided. Thymus 8 grams, 75% glandular, old and younger fibrous stroma with thick-walled vessels, no cortex seen, numerous Hassall's corpuscles mostly 8 and 9 and 12; also 6, 1, 2 and 7.

"AC"- Male aged 24, auricular flutter, thyreoid slightly enlarged. Thymus 80% glandular, vessels thick-walled, cortex and medulla in separate masses, haemorrhages into the gland. Hassall's corpuscles numerous, 3, 6, 7, 8, 9 and 12; few 1 and 2: a few eosinophils. Probably normal age involution.

"AP" - Male aged 49, an atypical case of lymphatic leucaemia, spleen 780 grams. Thymus 3·5 grams, only 7% glandular - very vascular - all blood vessels con-:tain excessive numbers of lymphocytes of large type - these cells also pervaded the thymic masses: some reticular cells and small lymphocytes also seen. No Hassall's corpuscles were seen in the sections, no eosinophils./

eosinophils. The glands showed the appearance of acute Hodgkin's disease.

Cases IX. - Male aged 17. - XXXIV. Female aged 19, XXXVIII. Female aged 43. - XLIX. Male aged 20, "V" - Female aged 60 :
were suspected of "B" but no evidence of regeneration of thymus found.

Case II. from A.II. Female about 50 years, anaesthetic death.

Thyreoid, irregularity in size and shape of vesi-:cles, very little pale-staining colloid in some, high columnar cells, masses of lymphocytes in inter-vesicular tissue resemble exophthalmic goitre. Supra-:renal, very little lipoid in cortex, congestion of inner layer of cortex. Zona reticulate with chrome cells almost replaces zona fasciculata. Lymphoid en-:largement in pharynx, spleen large and soft, large Malpighian Bodies, germ centres visible. Thymus about 7 grams, 75% glandular, both cortex and medulla present, well defined lying side by side, very vascular. Thick-walled vessels in fat and bands of pale hyaline fibrous tissue. Hassall's corpuscles numerous - all look "young", types 1, 2, 3, 7, 4 and 5 are represent-:ed. Small groups of eosinophils mono- and polymorphs and many basophils are present.

Mitotic figures were seen in pale epithelial cells of medulla, showing that this is regeneration - this in spite/

spite of her pelvic infection. The state of the thymus and her death are certainly due to the unsus-
hyper-
:pected/thyreoidism.

Case XXX from AI. - Male aged 24, cerebral abscess - well-developed, slight, 5 ft. 8 in., 10 st. 12 lbs. no feminism - no rickets, foetal lobulation well mark-:ed in kidneys and bicuspid aortic valve similar to case XXV. Heart small, 295 grams, and aorta narrow. Thyreoid weight 10·5 grams, nil abnormal: Parathyreoids nil abnormal: Suprarenal nil abnormal: Excess of lymphoid tissue all over body; tonsils and adenoids were removed at operation - no active tubercle found in lymph glands, calcification of mesenteric glands. Eosinophils seen in glands. Spleen 190 grams: Thymus 12 grams 15·5 × 3·3 × 0·4 cms. 45% glandular. Fatty infiltration of masses, medulla mostly with masses of lymphocytes beside it, large prominent reticulum cells in medulla - Hassall's corpuscles 1, 2, 7, 8, 10, 11, 4 and 5. A few clumps of mono-nuclear eosinophils, large mast cells in stroma and in medulla.

Case XXXVI. - Female aged 25, death after labour - fairly well developed, well nourished - Heart rather small, no evidence of rickets. Thyreoid, not appar-:ently enlarged, lobulation well marked, increased interstitial tissue and masses of lymphocytes, vesicles irregular in size and shape - very few contain any colloid/

colloid, piling of lining cells and ragged cells com-:ing off into lumen. Other masses show regular columnar lining cells. Suprarenal, general necrosis of both cortex and medulla except for a small patch of healthy cortex showing this is not a post-mortem change. Infiltration by red blood corpuscles and polymorphs and large mononuclears - these last two cells are also found distending the lymphatics in the capsule.

General lymphoid enlarhement, some old tubercle in glands, increase of cells in portal tracts of liver, spleen 180 grams: Thymus, 14 grams 60% glandular: thick-walled vessels in stroma, medulla more obvious than cortex which is in rounded masses beside it, very vascular, Hassall's corpuscles numerous, a few 8, many 1 and 2 and 7, large reticulum cells well-marked. Eosinophils in groups, very numerous of all types, many mast cells in medulla as well as in stroma.

It is probable that the lymphatism here is due to the hyperthyreoidism which is more than the hyper-:activity of pregnancy, rather than to the acute supra-renal deficiency which was certainly incompatible with life.

Case XXXVII.- from AI - Post-operative death. Male aged 15. Tall and slender, 5 ft. 4 in., 8 st. 2 lb. no feminism, no rickets. Heart and aorta small 175 grams. Thyreoid very irregular in shape, not enlarg-:ed - a strand runs up to hyoid, another from right lobe/

lobe down to thymus, normal pubertal histology - irregular vesicles, pale colloid with spaces in it, cubical lining cells, some piling and lying free on the colloid, intervesicular cells numerous. Parathyreoid, solid mass of cells, only one or two fat spaces penetrating the gland. Suprarenal small, weight of two together 5 grams, cortex narrow but cells full of lipoid. Chrome pigment present.

Great general lymphoid enlargement especially in stomach and intestine: many tuberculous glands in mesentery: spleen 105 grams, large lymph nodes, masses of lymphoid cells in portal tracts of liver with many eosinophils - the latter also present in pancreas. No abnormality in voluntary muscle.

Thymus 15·2 grams 12 × 5 × 0·7 cms. 80% glandular, well-formed fibrous tissue bands with thick-walled blood vessels - newer cellular fibrous tissue invading gland but no fat seen. Cortex and medulla irregular-:ily intermingled and about equal in amount. Hassall's corpuscles mostly large 8, 10, 11, 9 and many 12: also 1, 2, 7 and 3. Eosinophils present, not excess-:ive. A few mast cells present.

This thymus may be in a state of regeneration following the accidental atrophy caused by radium applied to his tumour a few months previously. It is not typical of age involution although the other organs are typical of early puberty.

Case XLV./

Case XLV.- Male aged 17, from A.III.-
Crushed between buffers: well-developed and nourish-:ed, 5 ft. 7 in., 10 st. Signs of feminism, fair skin, very slight moustache hairs, no hairs on chin or cheek, very little axillary hair, none on breast and pubic hair ends in a straight line (feminine), nothing abnormal about penis or testicles: no sign of rickets. Well-marked fat embolism in lung, heart small, 240 grams, aorta narrow, circumference 5·8 cms. above valve, 3·9 cms. above bifurcation, larynx 1·7 cms. antero-posterior. Liver, slight fatty change round central vein: many eosinophil polymorphs in portal tracts and in sinusoid capillaries. Kidney, nil abnormal. Thyreoid shows appearance of great activity, a few large irregular vesicles contain colloid with spaces in it, columnar or cubical lining cells, most vesicles empty with indented walls, doubl-:ing and piling of cells, vascularity great, no lympho-:cytes. This appearance, though resembling exophthal-:mic goître, is probably normal for his age.

Suprarenals small, largest weighs 2·5 grams, cortex narrow but zona fasciculate wall filled with lipoid, very little zona reticularis and composed of pink "full" cells. no lipoid confirmed in frozen sect-:ion.

Great general excess of lymphoid tissue especially cœliac and mesenteric glands but no gross or micro-:scopic/

microscopic tubercle, many eosinophils in glands - these are in excess in all the tissues even in the heart muscle: spleen large, 160 grams, with large lymph nodes, spleniculus similar. Thymus, 47·5 grams 16 × 8·4 × 1·1 cms. 95% glandular. Haemorrhage in right lobe probably due to the accident - thick whit-:ish fluid could be squeezed out of gland as in a child - a film was wet-fixed and showed the usual cells.

Thick-walled vessels in stroma, medulla, promi-:nent masses of cortex alongside. Hassall's corp-:uscles numerous, 8, 9, 10, 11 and 12; also 1 and 2. Eosinophils very numerous indeed, of all types, baso-:phils present. Many of the features of status lymphaticus in adults are present here.

Case IV. - Female aged 30 from AIII. - fall from a window ? suicide due to alcohol, moderate development, very fat - 5 ft. 1½ in., 10 st. Congenital absence of right ovary - uterus etc. apparently normal - heart small, 215 grams, subendocardial hæmorrhages.

Liver, advanced fatty change due to ? alcohol.

Thyreoid normal adult appearance.

Suprarenal, Chrome cells marked; Some general lymphoid excess, no tubercle, spleen 127 grams, large lymphoid nodes.

Thymus 17·95 grams, 11 × 2 × 0·5 cms. 60% gland-:ular; thick-walled vessels in fat, cortex and medulla well/

well demarcated. Hassall's corpuscles numerous, 1, 2 and 7, 3, 4, 6; also 8 and 10.

Case XIX.- Female aged 55 - from AIII. - Suicidal fall from a window, well-developed and nourished, 5 ft. 7 in., 10 st. 6 lbs.

Post-mortem.- Brain oedematous, no injury to skull, liver and kidneys fatty change, other organs healthy.

No general lymphoid excess, some large glands in cœliac region.

Thymus 6·4 grams, 35% glandular.

Thick-walled vessels in stroma, medulla and cort-:ex both represented, cortex in separate masses of lymphocytes. Very large reticulum cells in medulla, some almost giant cells.

Hassall's corpuscles mostly 1, 2 and 7; also 12.

A small cyst lined by cubical cells with oval nuclei and containing pink granular material was found.

No eosinophils seen - some mast cells.

Under/

Under the heading "C" are described thymuses from various cases under the following sub-headings:-

C.I. - Primary Atrophy - marasmus,(Dudgeon.)[6]

C.II.- Chronic Wasting Diseases and

C.III.- Acute Disease causing accidental atrophy or secondary atrophy.

C.I.- "Y" - Male aged 14 days, marasmus with thrombosis of aorta and numerous cortical infarcts in kidneys.

Thymus, weight 4½ grams (11·7 - 20·7, Bratton). Dudgeon[6] gives average 2·68, largest 5 grams for primary atrophy - Rühran[82] average 2·2 grams. - about 70% glandular, well-formed fibrous tissue and thick-walled blood vessels, no cortex seen, large pale reticulum cells are numerous, few lymphocytes and many large wandering mononuclears. Hassall's corpuscles very numerous, 1, 2, 3, 4, 5, 7 - a few partially flaky 8.

Eosinophils very numerous, mostly dark mononuclears, basophils numerous in stroma and in gland.

This child died so young that the typical appearances of a marasmic thymus are not all present - giant cells and large Hassall's corpuscles with calcification as described by Dudgeon are not present.

C.II. - Secondary atrophy also causes loss of weight. Dudgeon gives average 3 grams - largest 9·3 grams. Seven cases died of tuberculosis - unfortunately, only histological/

histological examination was made in most of these.

"B" - Female aged 3

"H" - Female aged 11

"A.F" Male aged 14½ and

"Z" - Male aged 22 died of tuberculous meningitis;

Case XXXI.- Female aged 58, of miliary tubercle;

"W" - Male aged 18, of glandular and extensive peri-:toneal lesions; "AN" - Female aged 3½, of acute obstruction by a tuberculous mass in colon (Thymus 9·8 grams, body 2 st. 12 lbs.).

No tuberculous lesions were found in any of the thymuses except that of "W", which was occupied com-:pletely by caseous masses with giant cells etc. and many acid-fast bacilli in the lesions. The remains of the thymus show well-formed fibrous tissue replace-:ment - a few Hassall's corpuscles, 1, 2 and 8 - no eosinophils.

In case XXXI. from the oldest patient only 2% glandular thymus persisted in the fat, consisting of cords of endothelial cells and clumps of lymphocytes - Hassall's corpuscles, type 8 only and no eosinophils.

Of the others, a description of the youngest "B" is sufficient as the others resemble it, mutatis mut-andis for differences of age.

About 50% well-formed fibrous tissue with thick-walled blood-vessels, no cortex is seen and few lympho-:cytes in the medulla; they are replaced by cells with dark elongated nucleus and by endothelial cells.

Hassall's/

Hassall's corpuscles very numerous indeed, 1, many 2, 3, 4, 5, 6 and many 7, many 8 and some 9. Eosino-:phils are present in normal numbers.

In all the other cases also, and in tuberculous gland involvement of the other cases, such as accid-:ents, the numerous calcified Hassall's corpuscles were a striking feature. Eosinophils were found in normal numbers in all - both Dudgeon[6] and Fortescue-Brickdale[12] refer to the absence or scarcity of these cells in the thymus of tuberculosis.

A case "A" - male aged 8 - chronic rheumatic heart disease with wasting, was examined. The suprarenal cortex contained almost no lipoid in the cells.

Thymus 75% glandular - pale stained hyaline fibrous tissue, vessels moderately thickened, mostly medulla with many Hassall's corpuscles, 8, 9 and 10 and a few 1 and 2. Eosinophils in normal numbers.

A remarkable section of thymus was obtained from a baby aged nine months "AB", who died of ? Banti's Disease. Thymus about 30% glandular, old and young cellular fibrous tissue, no cortex, few Hassall's corpuscles in the medulla of types 6 and 12, no young cellular forms seen, very few lymphocytes, cells with dark elongated nucleus and reticular cells - no eosino-:phils.

The most striking point is the absence of "young" Hassall's/

Hassall's corpuscles which have been found in almost every other case except in some in old age, where more sections might have discovered them.

Case XLII. - Male aged 17 - a renal dwarf - showed the combined effects of age and accidental atrophy . He died of acute nephritis superimposed on very marked chronic interstitial nephritis.

Thymus, 8·5 grams, 65% glandular, large engorged thick-walled vessels in fatty stroma invading masses of thymus in which only medulla is represented.

Hassall's corpuscles numerous, mostly 10 and 8, many 7, and 11 and often 1, 2, 3 and 6. No eosino-:phils seen, mast cells very numerous indeed, invading the medulla.

C. III. - Acute diseases also cause atrophy of the thymus - Dudgeon gives average weight 5·4 - larg-:est 14·0 grams.

"C" - Male aged $^{8}/_{12}$, pneumococcal meningitis. Thymus 85% invaded by cellular fibrous tissue, no fat, only medulla present, numerous Hassall's corpuscles, 1, 2, 3, 6, many 8 and 12 - many eosinophils.

"D" - Male aged $^{8}/_{12}$ - broncho-pneumonia - sudden death. Thymus 22 grams (26·8 Bratton) 100% - medulla and cortex both present and well demarcated, large thin-walled blood vessels in stroma; many Hassall's corp-:uscles/

corpuscles 1, 2, 3, and 8 (invaded by eosinophils). Eosinophils extremely numerous, mostly large pale nuclei.

Is this a case of Status Lymphaticus ?

"F" - Female aged $2\frac{4}{12}$ - broncho-pneumonia - 90% - thick-walled vessels in invading tissue, no cortex, Hassall's corpuscles 1, 2, 3, 4, 5, 7, 8 - few eosino-:phils.

"K" - Female aged 23 years, septic thrombo-phlebitis after abortion.

Thymus, about 2% only, small masses resemble in-:flamed lymph gland - No Hassall's corpuscles seen in section.

"L" - Male aged $2\frac{10}{12}$ - pneumococcal arthritis, operation, sudden death, diphtheritic membrane on fauces.

Thymus, weight 5·45 grams after fixing about 80% glandular, cellular invasion, some thick-walled vessels, fat invasion also, no cortex, very vascular, Hassall's corpuscles numerous, mostly 2, some 1, 7, 8, many 6 and 12, numerous eosinophil polymorphs.

Note this resembles C. II, closely but not Case XX given Page 49.

"N" - Male aged $6\frac{9}{12}$ - cerebro-spinal meningitis. Thymus, 13·6 grams, 90%, invaded by well-formed fibrous tissue with thick-walled vessels, no cortex, Hassall's corpuscles/

corpuscles numerous, 1, 2, 3, 4, 6, 7 a few 8, 11 and 12, eosinophils in normal numbers - again this resembles the thymus of chronic wasting disease closely except for less loss of weight.

"Q" - Male aged 40 - from A. I. - Lobar pneumonia. Thymus, 2 grams, 1% glandular, masses of reticulum cells, very few lymphocytes, Hassall's corpuscles, 2, 7 and 8, no eosinophils seen.

"AG" already described under "B".

"AK" - Female aged 8½, septic sinus thrombosis after chronic otitis media - wasted.
Thymus, weight 6·5 grams after fixing 50% glandular, mostly old fibrous tissue, some younger cellular, some fat, thick-walled blood vessels, very vascular and wide lymphatics, no cortex, Hassall's corpuscles numerous, 1, 2, 3, 7, few 8 and 11, eosinophils present but not numerous, basophils present. This should perhaps have been included under C.II.).

Case XX. - Female aged 10 - diphtheria, tracheotomy - from A. I. - Well-developed, 4 ft. 3 st., 12 lbs., large lymph glands in neck, mesentery and cœliac regions - not tuberculous - small abscess in neck below tracheotomy wound.

Thyreoid large isthmus, normal histology for her age, also parathyreoid. Accessory mass of thymus containing/

containing five Hassall's corpuscles, types 1, 2 and 3, lies inside capsule of parathyreoid against thyreoid.

Thymus, 27·5 grams (26·8) 80% glandular - thick fibrous strands with thick-walled blood vessels and fat; no cortex and few lymphocytes seen anywhere - great vascularity - many hyaline clots in vessels (similar in thyreoid); cells in medulla mostly large wandering mononuclears, some having phagocyted red blood corpuscles, many mitotic figures, many plasma cells with cart-wheel nucleus. The whole looks like an inflamed lymph gland without polymorphs. Hassall's corpuscles not numerous, 1, 2, 3, 4, 5 and 7 - a few eosinophils in groups, basophil mast cells in stroma.

"AH" - female aged 6 days may be included here - im-:perforate anus. Thymus 3 grams, 100% glandular, cortex and medulla well demarcated and equal in width, very vascular. Hassall's corpuscles in enormous numbers, crowded together amongst a syncytium of reticulum cells, mostly 1, 2, 5 and 7; also 3. Many eosinophils, mostly with large pale round nucleus, and tissue mast cells very numerous in stroma.

Encephalitis Lethargica was known to have occurred previously in three of the cases of sudden death - XXIII, XXV and XXXIII. Death was due in two of these to arterial disease, coronary in one, cerebral in the other. Both showed some excess of lymphoid tissue, one in the intestines, the other in pharynx and mesent-:ery/

mesentery; in both, the spleen was excessively large, 220 and 230 grams. The boy of 14, Case XXV. who was in the ward for post-encephalitic symptoms showed no particular lesion sufficient to cause death and was definitely lymphatic.

A brief comparison of "accidental" with age atrophy of the thymus here follows. Refer to "B" C.II and Case XV, A.III.

The replacing fibrous tissue rarely contains fat spaces in the first, always in the second; each strand of fibrous tissue penetrating the thymus has a few fat containing cells at its apex. Thick-walled vessels occur in both even when disease atrophy occurs in young children.

In age atrophy, the cortex is represented by round or oval masses of lymphocytes lying beside the irregular masses of medulla or embedded in them as in adult glands, where the lymphocytes are always found surrounded by rows of reticulum cells.

In disease atrophy at any age the cortex dis-:appears and few lymphocytes are found in the medulla.

Hassall's corpuscles appear to be much more numer-:ous in disease atrophy and are of all types but very frequently 6, 9 amd 12 - the calcified types are de-:scribed particularly in tuberculosis.

In age atrophy, most of the corpuscles are of the large flaky types 8 and 10, but young cellular ones are/

are found here and there in almost all cases.

The gradual reduction of eosinophils which occurs with age does not seem to be hastened by disease - nor do basophil tissue mast cells seem to increase very markedly.

In all cases of regeneration of the thymus, young cellular Hassall's corpuscles were found to be numer-:ous and often eosinophils increased both in the thy-:mus and in other tissues in cases of lymphatism.

These features have also been noted in several cases of lymphatism in the Pathology Department collect-:ion which I have studied. One of these, a sudden death, is a "Tranent Case" described by McGowan and McNeil[13].

Discussion/

DISCUSSION OF THE FUNCTION OF THE THYMUS WITH REFERENCES TO THE LITERATURE AND TO THE RESULTS OF MY RESEARCH.

The relation of the thymus to the endocrine system is of great interest, although the present position of the gland as an internally secreting body is so precarious that Schäfer[14] omits it from his later edition of The Endocrine Organs. He explains that as injection of extracts of thymus produce effects exactly similar to those of histamine and choline found in many tissues and organs, and as surgical removal gives negative results, the evidence for an endocrine function is no greater in the case of the thymus than in that of the spleen or lymph glands.

Marine, Manley and Baumann[15] after experimental studies on a large scale on the effects of removal of various endocrine organs on the thymus, while admitting the fact that in its physiological and pathological reactions it resembles the general lymphoid tissue, do not allow that this is a basis for excluding a poss-:ible internal secretion but rather indicates our lack of knowledge of this organ.

In favour of an endocrine function of the thymus is its epithelial origin from the caudal aspect of the 3rd and 4th gill pouches in close relation to the para-:thyreoids/

parathyreoids, and the anatomical relationship to these bodies and to the thyreoid - accessory thymus bodies from the 4th pouch being often found in the thyreoid (as in Case XX.) while accessory thyreoids or parathyreoids (common in the rabbit) are sometimes embedded in the thymus.

The epithelial cells give rise to a reticulum, (Hammar)[16], closely resembling that of the parathyreoid bud which is quite unlike the thyreoid,(Quain[17]).

This "primary thymus",(Spencer)[18], persists in some fishes secreting mucus, may appear as cysts lined with ciliated epithelium (in the kitten) or may be the source of tumours, as in that one described by Rolleston[19] which was partly a cystic adenoma of mucous glands, partly a haemorrhagic chondro-sarcoma and resembled a "parotid tumour".

The solid strands of epithelial cells persist as Hassall's concentric corpuscles till old age, and have the appearance of activity in all growing or regenerat-:ing glands, branching strands of pale syncytium being seen connected with undoubted concentric corpuscles. The very large bodies seen in some atrophied glands could hardly have attained their size when relieved of the pressure of lymphocytes around, by simply im-:bibing fluids; more likely they were laid down lay-:er by layer by the flattened cells surrounding them.

If in thymus regeneration only a lymphoid hyper-:plasia/

hyperplasia were called for, would not germ centres and lymph cords appear and crush aside the atrophied remnants of adult thymus with its calcified corpuscles till the whole resembled a typical lymph gland ? Whereas in these cases, small cellular Hassall's corpuscles in the pre-concentric stage are seen, (Gulland)[20], and one cannot resist the impression that the epithelial elements are also regenerating with the reticulo-endothelial. Hammar[16], who has worked so much on the thymus, regards it as an epithelial organ throughout life, having been secondarily invaded by lymphocytes of mesodermal origin. May it not be that the medulla and cortex of the thymus are as dis-:tinct functionally as those of the suprarenal, or as the parts of the pituitary or of the thyreoid-para-:thyreoid system. These all come into close anatomi-:cal relationship at an early stage of development, and may yet be found to interact in some way producing perhaps a synergic action of the pairs of autacoids.

The suggestion is offered that the epithelial elements of the thymus may produce an internal secret-:ion which governs the multiplication of lymphocytes throughout the body - a secretion perhaps travelling by the lymph stream from the thymus, as blood capill-:aries are not seen in close relation with this epith-:elium.

This is only one of the difficulties in the way of/

of this theory, the facts of embryology that lympho-:cytes are present in the body before they are seen in the thymus are rather against it, but are not in-:surmountable with the analogy of the suprarenal be-:fore one. It would explain the fact that general lymphatism is always associated with enlarged or per-:sistent thymus and also the observation that the cortex does not regenerate without the medulla. Hoskins[21] states that this does occur after thyreoid feeding but it was not noted in any of my cases of hyperthyreoidism, and prominent medulla as a sign of regeneration is seen in the Plates of Marine[15] of the thymus after suprarenalectomy, though changes in the Hassall's corpuscles are not detailed.

Another point in favour of some important funct-:ion for this "gland" is its constant presence and its shape as definite as that of the thyreoid - the heart-berg or bread, or the round - bread of the butcher - Hangsted[22] said "inter constantissima hominum organa est thymus". The "absence of thymus" noted[23] in a case of a child of nine months in a state of very poor nutrition shown by œdema and eccymosis and not veri-:fied microscopically was probably accounted for by the "primary atrophy" of marasmus, although it is definitely stated that there was "no fibrous tissue to mark the position of the absent organ". It has been missing in certain cases of acephalic monsters,(Simon[24]), and abnormally large in anencephalics,(Sanné[25] and others),/

others, and this association with foetal abnormalities brings it into relation with the internally secreting glands.

In the "tertiary thymus" of adult life, fat re-:places lymphoid tissue as it does the myeloid tissue in the shafts of long bones, or in the lymph glands of old age,(Gulland)[26], but the gland retains its shape, (Waldeyer)[27], and its power to regenerate all its ele-:ments in answer to the stimulus of lack of suprarenal or excess of thyreoid secretion and tumours arising from it in the anterior mediastinum "may by their shape at once recall the thymus"[28].

As for direct proof of internal secretion from the thymus this is lacking. In both feeding experiments and injection of extracts the effects are probably due to the nucleo-proteins of the lymphocytes which provide Vitamin "B"(McCarrison[29]), or cause intravascular clotting or a fall of blood pressure, none of which effects are of course specific to the thymus.

Could an injection of the primary epithelial thymus be made before the invasion by mesodermal ele-:ments, or, as Emrys-Roberts[30] suggests, could the re-:sult of injection of extracts derived from the poss-:ibly abnormal thymus of a status lymphaticus case be compared with those of its normal proto-type in healthy children or animals, we would be in a position to state whether/

whether or no the thymus produces an antacoid.

Thymectomy was said to cause changes in metabol-:ism especially in young animals affecting bone form-:ation, and the muscular and nervous system, causing a condition which McCarrison[29], quoting Tarulli and Lo Monaco's experiments, compared to the polyneuritis of his pigeons deprived of Vitamin "B". Abelous and Billard[31] noted a weak resistance to muscular fatigue and progressive paresis in the frog; Ver Eecke[32] thought that their fatalities were due to lowered re-:sistance to sepsis. Effects of thymectomy on the gonads have been noted. Parke and McClure[33] have shown that no appreciable result is obtained by re-:moval of the thymus, and lately Van Allen[34] and co-workers showed that ablation of the thymus in young, adult and old rabbits left the "operated animals com-:parable in all respects to intact normal rabbits", but they do not assume that the loss of the thymus is entirely without effect on rabbits even of mature age, and they find that differences in the reaction of these animals to inoculated neoplasm or to syphilitic in-:fection do occur although less definitely and to a slighter degree than after partial thyreoidectomy.

Experiments on the thymus of rabbits should be the more comparable with human conditions because in these animals the thymus is purely entodermal in orig-:in/

origin as in man, whereas in the guinea-pig it con-:tains both ecto- and ento-dermal components, and in the mole is purely ectodermal derived from the ductus prae cervicalis, and having, through a parallelism in development, acquired a similar structure,(Kastschenko)[35].

Perhaps the strongest argument in favour of an internal secretion for the thymus is the fact that the rare condition called myasthenia gravis is associated in more cases than could be explained by coincidence, with by tumour growth of the thymus. Weigert[36] suggested that this symptom complex may ultimately be attributed to an abnormally functioning thymus. The occurrence of Basedow's disease as an occasional complication links this condition with the other pluriglandular dyscrasias. Various minor anomalies but no constant pathological lesions are found in the spinal cord of which one - a group of ependymal cells beside the canal in the cervical cord[37] occurred in one of my A.II cases - XVII. The most constant finding is collect-:ions of lymphoid cells in the muscles and the sympt-:oms may be due to the degeneration of fibres which accompanies these lymphorrhages.

Whether one imagines hyper or hypo secretion of the thymus to occur when it is the site of a tumour, by analogy with the various pituitery and thyreoid tumours, there is some connection between thymus dys-:function and the production of masses of lymphocytes in abnormal situations in this disease. They are found/

found in the muscles, the liver, the adrenals, and occasionally the kidney and thyreoid and even the spinal medulla,(Mendelbaum and Celler)[38]. That these cannot be metastases from a malignant thymoma as suggested by Weigert[36] is discussed by these writers[38]. They point out that only small lymphocytes and occasionally eosinophils are found in these lymphorrhages and that they are found even when no thymic tumour is present or when this is a endothelioma incapable of producing lymphoid metastasis. Weigert[36] himself suggested the possibility that these cells represent a reaction to metabolic processes dependent on a perversion of thymic function.

The relation of the thymus to the gonads in both sexes is well established,(Calzolari)[39]. Henderson[40] noted that in castrated cattle the thymus is nearly double the size that obtains in normal animals. In all castrated animals the normal age involution is retarded but not permanently prevented, but gonadect-:omy has only weak powers of exciting regeneration in already atrophied thymus glands,(Marine, etc.[15]). Goodall[41] notes that the retarded atrophy is due to delay in fatty invasion, persistent lymphoid growth and delay in the process of disintegration of the epithelium composing Hassall's corpuscles.

On the other hand, Handerson[40] reported that the normal thymic atrophy of puberty was greatly hastened in/

in bulls used for breeding and in heifers which have been pregnant several months. Herring[42] showed that pregnancy in rats caused a very marked loss of weight of the thymus as compared with age control animals, and McCarrison[29] suggests that this may be due to the great call for vitamins in pregnancy reducing the store in the thymus.

The reciprocal effect of the thymus on the sex glands is not so obvious. There is some evidence that thymectomy hastens the onset of sexual maturity in rabbits, (Paton[43]), (Marine[44]). After thymectomy Klose and Vogt[45] obtained an increase in the rate of development of both testicles and ovary. This was confirmed for the testicle by Noel Paton[46] who found a definite increase in weight in young but not in adult guinea-pigs. No direct relationship between the size of the thymus and weight of the testis could be made out by this writer, but this did not surprise him because, as Goodall[41] points out, the size of the thymus depends rather upon the amount of lymphoid tissue than upon the development of its characteristic constituent - the Hassall corpuscle. Noel Paton[43] also found that removal of both thymus and testis markedly delayed the growth of guinea-pigs whilst no such result followed the removal of either gland alone. He noted[46] that in female animals thymectomy produced no effect on the length of time taken by the animals to/

to become pregnant, as compared with normal controls.

Blair Bell[47] reporting the results of öophorect-:omy in cats quotes Biedl's[48] opinion that the thymus inhibits the development of the ovaries.

Swale Vincent[49] in reviewing the experimental evidence is "tempted to the hypothesis that the thymus furnishes an internal secretion of some kind which ministers to the need of the economy before the repro-:ductive organs are fully developed. Normally, this internal secretion is provided by the testis or ovary after puberty".

The observations of Gudernatch[50] on tadpoles - that thymus feeding produces giant tadpoles which do not metamorphose, falls into line with the opinion quoted above, but we must remember that the thymus may be a more important organ in frogs than in higher vertibrates as it persists throughout life and is act-:ive in hibernation.

In this connection certain clinical aspects of status lymphaticus are interesting. Almost all ob-:servers are of opinion that poor development of secondary sex characters proper to the male is common-:ly found, signs of feminism after puberty have been described, such as slender long thorax, rounded arms and thighs, increase of sub-cutaneous fat, soft deli-:cate skin, scanty hair on lip and chin, sternal and axillary regions and a feminine distribution of pubic hair, external genitals poorly developed, some crypt-:orchids[51]. Status Lymphaticus is said to be six times commoner/

commoner in males than in females, but in the latter also "delicacy" of form and hypoplasia of genital organs has been described. Emrys-Roberts[30] denies this and describes three cases of persistent thymus in girls after puberty where no abnormality of the genitals was found - two of the patients were actually menstruating at the time of their sudden deaths.

At the other extreme are believers in the "Vago-:tonische Disposition" who find that the thymico-lymphatic state in women is associated with the de-:velopment of some male characters such as a triangle of pubic hair, etc., due to the inadequacy of ovarian secretion.

Of my cases one, Case XLV. a male of 17 showed lack of hair on face and chest and in axillae, and the feminine distribution of pubic hair, but he was well-developed and the genitals were normal - he was a case of A.III. and "B". Another little boy of 9 - Case XLVIII showed undescended testicle on the right side and a small penis - he had no status lymphaticus and the thymus showed the usual atrophy of inanition as he had lived four days after a fracture of the skull. Case IV. A.III and "B", had no ovary on the right side.

The next internally secreting organ with which the thymus is believed to be in interaction is the thyreoid. The close anatomical relationship has al-:ready been mentioned. Spencer[18] suggests that press-:ure on large veins at the root of the neck by an en-:larged/

enlarged thyreoid might cause venous congestion and enlargement of the thymus.

Collections of lymphocytes have a prominent place in the histology of the thyreoid in many conditions - exophthalmic goître, Riedles struma, the atrophy of insanity,(Schäfer[14]). Pathologically the thymus has been found enlarged in association with thyreoid dis-:ease in cases of exophthalmic goître,(Halsted[52]) myxœdema, cretinism,(Spencer[18]), and simple congenital goître,(Swale Vincent[49]). Basedow's disease has been associated with myasthenia gravis which is possibly a disease of thymus function, and in Status Lymphaticus enlargement and hyper activity of the thyreoid have frequently been described.

McNeil[53] states that the morbid anatomy of Status Lympha ticus in the child is identical with that of exophthalmic goître in the adult. Sudden death occurs in both diseases especially during the exhibition of an anaesthetic, and some surgeons urge the removal of the thymus either surgically,(Harberer[54]) or radiologically, (Webster[55]), when the thyreoid is treated.

Focal necrosis of the myocardium has been observed clinically in both syndromes, and such lesions have been described by Good Pasture[56] in rabbits fed on thyreoid and thereafter anaesthetised. Herring and Hoskins[21] noticed that such thyreoid-fed animals often died suddenly. Another possible cause of death is inhibition/

inhibition of the heart through the vagus which is hyperexcitable.

Experiments on animals prove that thymus hyperplasia follows thyreoid feeding even when there is loss of body weight - Kahn[57] on tadpoles, Hoskins[41] on rats. The thymus undergoes an increase in size in foetal animals after thyreoid feeding of the pregnant mothers - guinea-pigs,(Swale Vincent[49]).

Functional hyperactivity of the thyreoid at puberty and in pregnancy are, however, associated with involution of the thymus.

The two glands have been supposed to be antagonistic and the hyperplasia of the thymus in Grave's disease was looked upon as somehow compensatory, and good results were expected and sometimes obtained after thymus feeding,(Owen[58]). On the other hand, Bücher[59] quoted by Schäfer[14] who states that the result needs confirmation, claims to have produced symptoms of exophthalmic goitre in dogs by implanting human thymus in the peritoneum.

The effect on the thymus of hypothyreoidism is not so clear. Many records state that the thymus is enlarged in cretins and in cases of myxoedema and Schäfer[14] states that thyreoidectomy in young animals delays involution of the thymus while anaemia with lymphocytosis occurs. Marine[15] etc. proved conclusively, however, that thyreoidectomy hastens the normal involut-

involution of the thymus and that after removal of the thyreoid the thymus cannot regenerate even after combined suprarenal and gonadectomy. Hoskins[60] found that in thyreoidless tadpoles the thymus with other organs ceased to develop.

In one case of myxœdema, which I examined, there was no sign of persistence or regeneration of the thymus, whereas many of my cases confirm the relationship of hyperthyreoidism with regeneration of thymus, notably Case XXVII where complete regeneration had occurred in a woman of 48, but also in Cases II. XL. and XLVI. The association of pregnancy with an active thymus in Case XXXVI is probably explained by the condition of the thyreoid which closely resembled exophthalmic goître, exceeding the physiological activity of pregnancy. Herring[42] in pregnant rats found the thyreoid actually lighter in weight and showing no histological difference from the normal.

The activity of the thyreoid in Case XXIV - a female of 60 (associated with 20% of active thymus) may have had some relation to the starvation caused by persistent vomiting; it is very remarkable that such prolonged inanition should not have completed the atrophy of the thymus.

In a case of still-birth which occurred in the district practice of the Hospice in April 1924, the child/

child, a well-developed full-time male was born without difficulty or interference in a state of asphyxia livida and all efforts to start breathing were unavailing though the heart continued to beat for some time. At the autopsy performed by Dr. Jean Lorrain Smith, a large thymus "twice the normal size" was the only abnormality found.

The great interest of this case is that the mother, aged about 30 and a 3-para had suffered from myxœdema and had been treated with thyreoid throughout her pregnancy.

An association between the functions of thymus and parathyreoid might be expected from their close embryological relationship arising as they do, the one from the caudal, the other from the cephalad aspect of the 3rd and 4th gill pouches as buds consisting of a reticulum of syncytial epithelial cells. The lower parathyreoid, III. the "parathymus" may lie as low as the thymus - in ruminants it is commonly attached to the apex of the thymus which extends far forwards. (Schäfer)[14]. A parathyreoid has quite commonly been found in this position in my cases, more frequently on the right side.

In later life both glands are gradually infiltrated by fat - bearing connective tissue from the age of 22 in the parathyreoid (Cooper)[9] and the capillary blood supply of both especially the parathyreoid remains/

remains extremely rich and intimate even in old age.

In both glands eosinophil myelocytes and leuco-:cytes are present in the connective tissue strands, and also basophil tissue mast-cells, but the former appear to increase in numbers after puberty in the parathyreoid in contradistinction to the sequence in the thymus.

Experimental evidence of the effect of para-:thyreoidectomy on the thymus is lacking. Marine[15] showed that the parathyreoid factor was eliminated in his thyreoidectomies in rabbits.

The propensity to tetany is one of the most im-:portant clinical signs of rickets, and rickets is very frequently associated with lymphatism (Dudgeon)[6] and others. The laryngismus of rickets when it was found to be associated with a large thymus received the name of "thymic asthma" (Kopp)[61], but this symptom was placed with the other signs of a general nervous irritability by Escherich[61].

The thymus was thought to be connected with calc-:ium metabolism by Klose and Vogt[45], and Soli[62] stated that extirpation of the thymus in adult hens caused them to lay eggs without shells.

An abnormally "old" parathyreoid was found in Case XVI, a boy of 8 with lymphatism; otherwise noth-:ing abnormal was found in these glands. It was not-:ed that colloid vesicles were seldom seen - only mark-:ed/

marked in one case XXIX, a reason probably being that the inferior parathyreoid was most often found and it shows this change less frequently than the superior one (Cooper)[9].

In histological structure the thymus resembles the epiphesis cerebri more than any of the other endo-:crine organs (Osler and McCrae)[51] and the pineal has also been associated with the sex glands.

With the hypothesis a clinical relation has been made out. Persistence of the thymus has been des-:cribed in acromegaly (Erb, etc.)[63], but this occurs less frequently than hypertrophy of the thyreoid and parathyreoids, etc. and might be secondary to the former or to hypoplasia of the sex glands. Harvey Cushing[64] speaks of the pituitary as "this amazing structure which conducts the endocrine orchestra" and says that all hypophyseal disorders are pluriglandular. Death may occur suddenly in acromegaly (Brouardel)[1].

Perrier[49] noted changes in the pituitary after thymectomy, and changes in the growth of bone are said to have occurred from lack of thymus[45].

Dowd[65] under the title Hypoplastic-Dyspituitary type of child describes some cases of status thymico-lymphaticus.

No abnormality in the pituitary was noted in the few cases in which it was examined.

The association of the thymus with the suprarenals in/

in disease is perhaps its most striking relationship and recent careful experiments have confirmed clinical findings.

Addison[66] did not mention enlargement of the thymus in describing the disease which bears his name - this association was first noted by (Star)[67] in the case of a girl of 17 who died suddenly. Wiesel[68] and others established the association.

A white rat which survived suprarenalectomy by Harley about 1856 (Schäfer)[69] showed enlargement of lymphatic glands, and Crowe and Wislocki[70] conclude that "the most striking feature at autopsy on an ani-:mal with a long-standing adrenal insufficiency is the enlargement of -- lymph glands, and not infrequently there is also a hyperplasia of the thymus".

The recent work of Marine, Manley and Baumann[15] on rabbits and of Jaffe[71] on rats conclusively proves that suprarenalectomy is the strongest stimulus for increased growth or for regeneration of the thymus and other lymphoid tissue in young, adult and old animals, and, moreover, that this enlargement of the thymus occurs in spite of previous pregnancy or of great loss of weight and chronic infections which are features of suprarenal insufficiency, and all which conditions usually hasten involution. These workers hold that it is the interrenal or cortical system which is im-:portant, whereas Wiesel[68] believed that the chroma-:ffin/

chromaffin system was at fault and was responsible for the symptoms of Addison's disease and also for the hypoplasia of heart and blood vessels found in Status Lymphaticus in which the suprarenals are generally small. But Swale Vincent[72] does not believe that the normal tone of the blood vessels requires adrenaline, "there is indeed no reliable evidence that under norm-:al conditions the circulating blood contains any ad-:renaline at all".

In favour of the cortical effect on the thymus are observations on human infants in whom spontaneous cortical involution (Elliott and Armour)[73], associated with lymphoid hyperplasia occurs normally soon after birth, and on anencephalic monsters in which lack of fœtal cortex is accompanied by a large thymus.

Conversely, by feeding suprarenal cortex to ani-:mals(Hewer)[74] hastened thymic involution, and Herring[42] observed 12% increase in weight in the suprarenals in pregnancy with 52% loss in weight of the thymus.

Jaffe[71] accounts for the sex differences in rats' thymuses after suprarenalectomy - females' larger than males'-by the fact that there is a marked difference in the size of the suprarenals in rats, those of the female being much larger.

The thymus atrophies and the suprarenal cortex enlarges in conditions of starvation or avitaminosis with great constancy (McCarrison)[29] and the adrenaline content of the gland is also increased in these cond-:itions/

conditions.

The effect of suprarenal on thymus may be an in-:direct one through the thyreoid. According to Marine and Baumann[75] the cortex of the suprarenal exercises an inhibiting influence over the thyreoid while the medulla produces excitation.

Marine[15] found that thyreoid secretion was nec-:essary for the hyperplasia of the thymus after supra-renalectomy, etc.

Tendency to sudden death - the principal symptom of Status Lymphaticus may be related to the hypofunct-:ioning of the suprarenals - as Dale[76] noted that suprarenalectomised cats, even before they exhibit any symptoms, are very sensitive to the blood pressure de-:pressing effects of histamine - ten times more so than normal animals; and Lewis[77] found that rats, though they survive the operation, are made much more sensi-:tive to toxic substances than normal rats; they are also much more readily fatigued and stand further oper-:ations very badly and often die after fighting or struggling[71].

McGowan and McNeil[13] note that the course and prognosis of infections due to the pneumococcus were entirely altered in a school where Status Lymphaticus appeared to be "endemic", patients dying in the con-:gestion stage of pneumonia.

In/

In this research Addison's disease was suspected but not found in two cases "V" and "XL".

Small suprarenals with thin cortex were found in several cases of "B" - XLV, XXXVII, XXVII in particular, and although no definite changes in hist-:ology were found in all cases, frequent mention was made of a poverty in the cells of the zona fasciculata in lipoid or of irregularity of columns in this zone. No changes were noted in the medulla.

In case XXXVI an acute necrosis of the suprarenal was present but could hardly account for the lymphat-:ism unless it had been superadded to some chronic disease.

Pituitary, thyreoid and adrenal secretions all affect the metabolism of sugar and excess of carbo-hydrate in a diet deficient in vitamins - has been shown by McCarrison[29] to produce marked effects on the suprarenal. Presumably also the thymus being the "barometer of nutrition" would register the changes which occur in association with dysfunction of pan-:creatic secretion both internal and external.

Some recent work has suggested that blood sugar is low in cases of Status Lymphaticus[78] but Osler and McCrae[51] advised reduction of sugar and starch in the diet of children suspected of lymphatism - whether this treatment is merely on general principles is not stated.

Although/

Although there is no evidence that the vegetative nervous system is normally under endocrine control, the following description of the condition known as Vagotonia, (Eppinger and Hess)[79] is remarkable for the features which recall Status Lymphaticus :-

> "Usually nervous, pale-faced, greasy skin, sweating occurs readily, pulse rate slow, adults liable to asthma and eosinophilia, children to laryngismus stridulus. There is often hyper-:trophy of the tonsils and of lymphatic tissue throughout the body -- Vagotonia in recovery from disease -- and in sleep".
>
> (Lymphatic patients die during convalescence and in sleep).

M. Laignel Levastine[80] added to his description of Vagotonia the following :-

> "Sometimes signs of thymus persistence -- sometimes a subject experiences a sort of momentary arrest of the heart and the least effort may suddenly set up a considerable tachycardia or the inverse phenomenon. The aorta often appears narrow on examination with X Rays".

Compare with these a description by Buxton[81] of the features which should suggest Status Lymphaticus to an anaesthetist :-

> "Young persons, tall and weedy, skin fair, pale -- pasty, temperament, a curious blend - slow but highly intelligent, shy and self-conscious -- intolerant of cold -- pulse normally very slow, 50 to 60 and found to be rendered quick and irregular by some trifling occurrence which may have annoyed them -- blood deficient in haemo-:globin and lymphocytosis".

Most, if not all, endocrine diseases are poly-:glandular dyscrasias and in these various complexes the/

the thymus grows larger or smaller sometimes with great rapidity. Jaffe[71] records that hyperplasia probably begins within twenty-four hours after supra-:renalectomy. The fact that the thymus does not always record the state of nutrition, as in emaciated cases of exophthalmic goitre or Addison's disease, may indicate for it something more than the passive function of subcutaneous fat.

The thymus is certainly intimately connected with nutrition although the removal of it has not been found to affect growth - the early work of Klose and Vogt[45] on 'cachexia thymopriva' not being confirmed (Paton, etc.)[43].

The large size attained by tadpoles on a diet of thymus might be due to the richness of this tissue in good biological proteins in the nuclei of the lympho-:cytes rather than to a specific growth-producing sub-:stance.

The thymus is the first organ to show the effects of inanition and especially of deprivation of Vitamins - even of Vitamin B alone (McCarrison)[29] - this change may, of course, be secondary to functional changes in other organs especially the suprarenal.

McCarrison[29] thought that although the thymus might be a storehouse of vitamins for the body, it was quickly exhausted of its store, if vitamins were with-:held from the diet and it was not a specific remedy for/

for the symptoms of avitaminosis.

In young children Rühran[82] decided that a look at the thymus under the microscope was all that was necessary to form an opinion on the state of nutrition.

The thymus may be the only organ affected in cases of marasmus and it shows marked but different changes - secondary atrophy when death is due to chronic wasting disease, and in acute disease or rapid starvation it may show a similar type of degenerative change or marked loss of weight may occur without histological changes. It has been noticed by butchers that oxen driven under the yoke had a smaller thymus than animals of the same age who were not overworked.

If one could read the riddle of the Hassall's corpuscles to perfection, it might be possible to say by examining the thymus of a young adult, at what age and how seriously he had been ill in childhood as well as the age, state of development and state of nutrition at the time of death.

But the barometer is out of order in some cases, as when the "scrofulous" is superimposed on the lymphatic diathesis (McNeil)[53]; when a pregnant woman has Graves' disease, my case XXXVI perhaps; or a boy wastes with tubercle of the suprarenals (Emrys-Roberts)[30].

Some have thought that Status Lymphaticus is a deficiency disease due to lack of some essential factor in nutrition. In favour of this is its frequent association/

association with rickets (Dudgeon)[6], and its occurr-:ence in endemic form in industrial schools (McGowan and McNeil)[13], (Duncan)[83], etc.

Investigation in the Tranent School brought out the facts that the boys were subjected to crowding and lack of proper warmth in winter, and possibly to food deficiencies as "the diet had been improved late-:ly".

The occurrence of several cases in one family might be due as well to similar environment and food as to heredity, as this familial incidence of rickets and bovine tuberculosis is also noted.

Status-Lymphaticus is not restricted to any class - badly balanced diets are given to rich children as well as to the poor. It has been shown recently that excessive Vitamin A added to a diet poor in other Vitamins produces anaemia with leucocytosis and atrophy of the heart[84].

The lymphatic system is intimately related with fat metabolism - the thymus nearly trebles its weight during the last month of intrauterine life (Friedleben)[10] while fat is being laid down in the tissues, but that the increased size of the thymus is not entirely due to its lymphoid constituents is shown by the fact that the volume of Hassall's corpuscles in a young child is more than equal to that of the whole thymus of a foetus (Wallisch)[85].

Owen[58]/

Owen[58] suggests that "what is known of the thymus points to its function being to prevent emaciation as is evidenced in its enlargement in hibernating animals in which the thymus persists throughout life".

Apparently the cortex - the lymphoid part is the first to atrophy in disease and the Hassall's corpusc-:les seem the most resistant elements as Hammar[16] noted; they are increased in numbers and enlarged in wasted glands, but fewer young cellular forms are pre-:sent, most being flaky or calcified and completely degenerated.

In Recent Advances in Haematology (Piney)[86] says "the thymic reticulum cannot be regarded as being of epithelial origin but must represent the lymphocyto-:poietic mechanism of the organ". The relation of this gland to the blood-forming tissues removes it from the category of the endocrines for none of the others with the exception perhaps of the parathyreoid with its eosinophils is known to take part in blood formation.

In childhood normally there is relative lympho-:cytosis and this is associated with a functioning thymus and active lymphatic glands. If these persist into adult life or regenerate, as the result of exoph-:thalmic goître for instance, or if they undergo an unphysiological hyperplasia in lymphatic leucaemia, lymphocytosis again appears.

There is some evidence that acute leucaemia occurs most/

most commonly in constitutionally peculiar persons, (Jagic and Schiffner)[87]. Ewing[86] believes that the greater malignancy of some cases of Hodgkin's disease is associated with involvement - possibly primary - of the reticulum of the thymus.

My case "J" of lymphatic leucæmia showed a re-:generated thymus without, however, much evidence of activity on the part of Hassall's corpuscles.

"AP" showed thymus remnants overgrown by large lymphocyte cells - the glands and spleen of this case resembled acute Hodgkin's disease but obviously there was a great excess of lymphocytes in the circulating blood.

Leucocytes are already present in the embryo be-:fore the lymphoid "transformation" of the thymus so that the thymus cannot be the original source of leuco-:cytes as suggested by Beard[88]. The origin of the small thymic cells and their nature has been much dis-:cussed - Swale Vincent[49] states four theories. Prob-:ably the one held by Hammar[16] is correct, that is:- That the thymus remains an epithelial organ but that lymphoid elements have invaded it. That the small thymic cells are true lymphocytes was shown by Danch-:akoff[89].

It would be interesting to experiment on the relation of the thymus to the lymph glands, in order to see whether hyperplasia of lymphoid tissue all over the/

the body could still occur in hyperthyreoidism or in hypointerrenalism in the absence of the thymus.

The spleen is usually associated in the lymphoid hyperplasia which might be due to an autacoid from the medullary epithelial cells of the thymus.

Emrys-Roberts[30] only noted enlargement of the spleen in a few cases but it was noted in almost all my lymphatic "B" cases, such as - XXI, XXV, II, V, XXVII, XXXV, XL, XXX, XXXVI, XLV, the Malpighian bod-:ies being increased in number and size in all these cases.

Splenic atrophy follows later the involution of the thymus caused by vitamin starvation (McCarrison)[29]. On the other hand, thymectomy has been said to promote a compensatory increase of splenic follicles.

Splenectomy has no effect on the size of the thymus (Marine)[15].

The enlarged lymph glands in several of Emrys-Roberts[30] cases were haemolymph glands.

Anaphylaxis due to necrosis in lymphoid tissue has been supposed to be the cause of the sudden death in lymphatism in patients sensitised by intermittent lymphotoxaemia (Blumer)[90].

The thymus is also related to the granular leuco-:cytes and especially the eosinophils which are philo-:genetically and embryologically next in age to the lymphocytes (Gulland)[20]. Dudgeon[6] described two mono-:nuclear/

mononuclear types, and transitionals and polymorphs and says that these in the thymus differ from those in the marrow and blood in the smaller size of their gran-:ules. If they are related to the circulating eosino-:phils as seems likely from their distribution round blood vessels in the thymus (they are not so often seen inside the blood-vessels as in the parathyreoids[9]) one would expect a constant eosinophilia in healthy children and marked eosinophilia in Status Lymphaticus, Graves' Disease, etc.

In children as Dudgeon[6] points out, even thread worms can give rise to an eosinophilia. In rickets, so often associated with enlarged thymus, 20% eosino-:philia is described by Hock[91]. Eosinophilia occurs in adults of the vagotonic type, and in them the thymus is said to be often persistent. Eosinophilia occurs in Hodgkin's disease and in Addison's disease,(Swale Vincent)[49] and eosinophils are found in the lymphorr-:hages of myasthenia gravis (Hun)[92]. Piney[86] speaks of an increase of lymphocytes in the blood, and often of eosinophils during menstruation.

The observation was made in many of my cases that eosinophils were not only common in enlarged thymus glands but also in other lymphoid structures, in the portal tracts of the liver and occasionally in the stroma of kidney, pancreas, lung and thyreoid. - See cases/ XXI, XXV, XL, XXXVII and XLV.

In case XXII - a female aged 63 - who had had protein/

protein shock therapy for rheumatoid arthritis the week before her death, eosinophils were found in the 7% glandular thymus.

Dudgeon[6] has never found eosinophils in the thy-:mus of old people or animals. Eosinophils certainly decrease in numbers in the thymus as age advances while as Cooper[9] points out they increase in the para-:thyreoid. Basophil tissue mast cells occur in both glands' stroma and increase with age, but they were found in some of the very youngest thymuses I examined. They are supposed to replace the eosinophils in cases of tuberculosis (Fortescue-Brickdale)[12] but this was not found in my cases.

Metchnikoff[93] associates eosinophils with nutrit-:ion and believes they contain reserve materials simi-:lar to yolk granules.

The relation of the thymus to the red blood corp-:uscles is not so clear. Some have described nucleat-:ed red corpuscles in the thymus and these are certain-:ly present in the foetus (Cooper)[9]. Tarulli and Lo Monacco[29 & 49] described anaemia and lack of haemoglob-:in in animals after thymectomy.

On the other hand anaemia of a chlorotic type, (Paltauf)[5] is supposed to be a feature of Status Lymph-:aticus in which lymphocytes proliferate in the bone marrow.

Anaemia occurs in certain endocrine diseases associated with a large thymus - acromegaly, Addison's disease/

disease. No anaemia was present in a case of this disease in which only moderate regeneration of the thymus was present (Hewer)[94].

Pernicious anaemia has been said to be associated sometimes with a persistent thymus but this was not found in several cases of this disease which appeared at post-mortem during my research.

Blood counts of cases of genuine Status Lymphati-:cus must be rare - presumably it might not be safe to prick such a patient.

An article in the B.M.J.[95] mentions one where lymphocytosis and eosinophilia were found - the latter indicating worms.

My case XXI was noticed during life and at post-mortem to be of a waxy pallor - this could not be accounted for by the small quantity of blood in his stomach.

Differences in coagulability of the blood have been described in these cases. Some thought death was due to intravascular clotting, but Dudgeon[6] finds no evidence of this in any case. On the other hand, Brouardel[1] described petechial haemorrhages on the pleura and on the surface of the thymus. Neither of these conditions has been noted in any of my series.

Acland[6] found a peculiar condition of the Hassall's corpuscles in purpura and haemophilia not confirmed by Dudgeon[6].

One case XXXVII of post-operative death in which great/

great lymphoid excess was found, was examined twice by me in the course of the coagulation-time experi-:ments. There was no abnormality before operation, but marked shortening after it, probably due to cyan-:osis and shock. No ante-mortem intravascular clott-:ing was found at the post-mortem.

Gallatti[96] insists on the tendency to subcutan-:eous œdema in Status Lymphaticus - Ohlmacher[96] on pulmonary oedema. The former condition was not noted in any "B" case - the latter was present and probably due to the anæsthetic in Case XXI.

Changes in the heart and vessels have been noted in cases of lymphatism and the low blood pressure associated with a hypoplastic condition of the circul-:atory organs was supposed to predispose to fatal syn-:cope.

The non-specificity of the fall in blood pressure caused by thymic extracts has already been alluded to.

The suprarenal medulla when secreting in excess causes raised blood pressure, hypertrophied heart and thickened vessels as in some cases of experimental arterio-schlerosis (Roger and Gauget)[49]. Wiesel[68] believed that a lack of the physiological amount of this secretion is associated with hypoplasia of heart and vessels.

Certain experiments on puppies quoted by Swale Vincent[49] where enormous dilatation of the heart occurr-:ed after thymectomy suggested that the thymus was antagonistic/

antagonistic to the suprarenal so that after its re-:moval predominance of adrenal activity and hypertonus of blood vessels with dilatation of the heart occur.

Another possibility is that congenital abnormal-:ity accounts both for the narrowing of the aorta and thinness of its middle coat (Brouardel)[1] and for the lymphatic diathesis. Against this is the fact that these circulatory abnormalities are seldom found in lymphatic children such as the cases of sudden death recorded by Dudgeon[6], but in young adults in this "status" they are fairly common, pointing perhaps rather to a lack of essential food factors which "are essential for the perfect nutrition of the heart" (McCarrison)[29], especially in connection with the "effort syndrome" during the exacting period of adoles-:cence.

Cerebral haemorrhage due to rupture of the hypo-:plastic arteries has been suggested as one common cause of death in Status Lymphaticus (Osler and McCrae)[51].

One of my cases XLIV to be mentioned below showed the rare association of injury to the head with <u>intern-:al</u> cerebral haemorrhage without laceration of the surface or disease of cerebral arteries, moreover petechial sub-endocardial haemorrhages occurred in the left ventricle although the body was uninjured. Many of the accident cases and case XXXVII, post-operative death, showed these sub-endocardial haemorrhages.

In/

In three consecutive accident cases in my series, the small calibre of the aorta in comparison with the well-developed body was remarkable.

Case XLIII - male aged 21, 6 ft., 12 st. 4 lbs. - Heart 370 grams, spleen 160 grams, aorta circumference just above the valve 5·1 cms., above bifurcation of abdominal part 4 cms. - Thymus 11 grams, 75%, no lymphoid excess.

Case XLIV - Male aged 22, 5 ft. 9 in., 9 st. 11 lbs. Heart 270 grams, spleen 190 grams, aorta at some places 5·5 cms. 3·4 cms. Thymus 1 gram, 75%, lymphoid ex-:cess in mesentery.

Case XLV - Male aged 17, 5 ft. 7 in., 10 st., heart 240 grams, spleen 160 grams, aorta 5·8 cms. - 3·9 cms. Great general lymphoid excess. Thymus 47·5 grams, 95% - signs of feminism.

Cases XXX (A.I and "B") and XXV (A.II and "B") both showed congenital abnormality of aorta valve. Aorta above valve in the latter, 4·75 cms.

A very narrow aorta was found in case XLII, a "renal dwarf", male aged 17, 4 ft. 11 in., 5 st. 1 lb. marked chronic interstitial nephritis. Aorta $\frac{3}{4}$" and $\frac{1}{2}$" - Lymphoid enlargement of para-aortic glands, but thymus showed secondary superimposed on age atrophy, 8·5 grams, 65% .

Case XXXVII, male aged 15, B heart 175 grams, aorta small.

Disease/

Disease of the heart may also be associated with Status Lymphaticus. Brouardel[1] describes sudden deaths in cases of infantilism in city-bred children where there was marked fatty loading of the heart as well as other tissues.

Diffuse fatty degeneration of the heart muscle and of the liver was noted in Case XXXVII., post-operative death with lymphatism.

The myocardial degeneration of hyperthyreoidism has already been mentioned. It may have been the cause of death of Case II under chloroform, also per-:haps of Case XXXVI. after labour and anæsthetics, but no lesions were found in the pieces of left vent-:ricle wall examined. These lesions are more common in the right ventricle (Goodall and Rodgers)[97].

Status Lymphaticus has been associated with in-:sanity and is supposed in its minor degrees to be more frequent in the wards of asylums for the insane and for drug addicts than among the general population (Emerson)[98], and (Major)[99]. Lymphatism is described as having a psychology of its own "a curious blend - slow but highly intelligent, shy and self conscious, unduly affected by physical and moral stimulation, highly emotional but maintain an outward calm"[81] - just the type, in fact, to be killed by sudden grief or joy or pain by inhibition. They are the people, perhaps, who died suddenly on the table before or immediately after/

after the skin incision was made in pre-anaesthetic days - deaths which would afterwards have been attrib-:uted to the anæsthetic (Sir J.Y.Simpson)[100] and they are more prone to death by suicide or accidents and more predisposed to acute infections by their alcohol-:ic habits and less able to resist them than normal people.

Timme[78] suggests that migraine is associated with Status Hypoplasticus- or Lymphaticus - the pain being caused by pressure in a congenitally small sella turc-:ica of a pituitary undergoing compensatory hyperplasia to overcome the inadequacies of the individual.

Cases IV and XIX, both alcoholic, and dying of suicidal falls from windows, showed considerable per-:sistence of thymus.

"AG" - a mentally defective woman also showed a 75% glandular thymus more atrophied by the acute dis-:ease of which she died than by normal age involution.

It was noted that some of the largest thymuses in the whole series were taken from accident cases, and the frequency of lymphoid excess and foetal ab-:normalities in these cases has been mentioned.

Two questions arise - Are these to be considered as normal controls ? and is lymphatism a predispos-:ing factor in the causation of accidents ? Emrys-Roberts[30] described a case of persistent thymus in a girl of 19 who died of a street accident. He says "it is easy to say that if a thousand healthy children and /

and young adults were knocked on the head a large pro-:portion, if not the vast majority, would be found to possess enlarged thymus glands, but the safety of the statement is only equalled by its impracticability".

Borst and Grace[51] found lymphatic hyperplasia in 56% of 2000 men killed in action and in 86% of those aged 19-20 which would seem to show that this is the normal condition in healthy young adults and only people dying of disease are not "lymphatic".

In Report 34 of the(Industrial Fatigue Research Board)[101] it is stated that "the importance of the personal factor in accident causation is difficult to exaggerate since over 80% of all accidents have no mechanical origin and not more than 5% can be attrib-:uted to factors outside human control".

Youth and inexperience of course contribute but the "average number of accidents is found to be in-:fluenced by a comparatively small number of multiple accident people, individuals with an innate tendency to sustain accidents" and the same people who have acci-:dents in factories have accidents at home. The "number of accidents and number of times sick is posi-:tively related".

It is questioned "how far a tendency to sustain minor accidents may be taken as a criterion of a tend-:ency to succumb to major accidents".

There is great interest in the fact that Case XVI, a boy of 8 years, was run over and killed just outside the/

the gate of the Infirmary from which he had been dis-:charged after treatment of a fracture of the humerus sustained six weeks before in a run-over accident - he showed lymphatism.

No signs of previous minor injuries were noted in any other fatal accident cases in this series.

It was noted that several of the lymphatic cases had had previous operations without ill effect - this is a well-established fact about anæsthetic deaths - the patient may have survived a previous more severe operation - Article in B.M.J.[95].

Operations were responsible for ten deaths in my series - three died under the anæsthetic, Cases I, II and AA, while XXI, XXX, XXXVI, XXXVII, L, O and AN died soon after operation.

It is remarkable that five of these or 50% were definitely lymphatic while in Cases I and O no definite cause for death was found.

The relation of the "scrofulous" to the "lymphat-:ic diathesis" has been discussed by Dr. McNeil[53]. He points out that in Germany the idea of diathesis in connection with tuberculosis persisted even after the discovery of Koch's bacillus and when hereditary tub-:ercle was not proved. It was taught that scrofula and lymphatism were associated and in cases of status lymphaticus the tuberculin reactions were unusually severe.

McGowan/

McGowan and McNeil[13] found 59% of boys, in a school in which they believed Status Lymphaticus to be endemic, reacted to cutaneous tuberculin test as against 14% in a control school. He states that this abnormal constitution is also found along with and probably explains certain rare fulminant types of many other infections such as pneumococcal. Boys at this school were found dead in the morning having gone to bed well - the lungs were in a state of congestion, the earliest stage of pneumonia. Rapid fatalities of this sort from a paratyphoid infection occurred in a Preston School (Duncan)[83] and many diseases of child-:hood, such as scarlet fever, measles, chicken-pox and diphtheria (Dant)[13] may take on a fulminant course in lymphatic children. Whooping-cough has also been re-:lated to Status Lymphaticus (Adkins, etc.)[102].

Of my lymphatic cases, there was evidence of tubercle in V, XXI, XXV, XXX, XXXVI and XXXVII and in XVII and XXVI but in none of the cases dying of tuber-:culosis except perhaps Case V was lymphatism a feat-:ure.

Of acute diseases "D" succumbed suddenly to acute broncho--pneumonia and the thymus, though under weight,-showed no fibrosis.

Much has been written about enlargement of the thymus in babies (Jackson)[103] and others - the condit-:ion was found radiologically in 40-50% of new-born babies/

babies by Peterson and Miller[104].

The symptoms produced, such as, Holding Breath Spasms, Syncope, Cyanosis, Cough, Noisy Nasal Breath-:ing, Choking attacks (Morgan, etc.)[105], are brought on by attitudes in which the trachea would be pressed on by the thymus at the inlet of the thorax and as cure has followed the passage of a long tube (Jackson)[103], or removal of the thymus by operation or partially by X Rays[105], there can be little doubt that the symptoms are often due to an enlarged or peculiarly shaped gland. This must be quite a different condition, however, from Status Lymphaticus as these children stand severe operations and difficult anæsthetics quite well (Emrys-Roberts)[30], and if death does occur it is obviously due to asphyxia.

Case "G" may have been such a condition, but apparently no symptoms were noted before death.

The still-born boy we attended from the Hospice had probably another cause of enlarged thymus - his mother's endocrine condition. (See Page 66-67)

SUMMARY/

S U M M A R Y.

The cause of Status Lymphaticus is still unknown - the following are the main hypotheses which have al-:ready been discussed under various headings :-

1. That Status Lymphaticus is an hereditary condit-:ion due to congenital abnormality of the endo-:crine organs.

2. That it is an acquired disease due to faulty nutrition in childhood - this perhaps acting through the endocrine system.

3. That it is due to chronic infection.

4. That it is caused by faulty nutrition or chronic infection having called forth a lymphatic re-:action in persons predisposed to it by heredi-:ty or endocrine dysfunction.

5. That it is not an entity at all, but a syndrome produced by diseases of other endocrine organs.

6. That it is a "Blood Disease" - comparable to chlorosis or lymphatic leucaemia.

As the theory which one is to adopt depends so much on the function which one holds to be discharged by the thymus gland itself, the literature on this subject has been reviewed to some extent.

CONCLUSIONS.

The value of conclusions based upon a short series of cases is of course doubtful, but the following im-:pressions have been collected from a study of these cases.

1. That cases of sudden death are occasionally associated with persistent thymus in adults and with a large thymus and excessive lymphoid in children.

2. That minor degrees of Status Lymphaticus occur rather frequently - or else

3. that a certain degree of lymphatism is the normal condition at certain ages as revealed by accidental deaths.

4. That persons dying of accidents - especially street and industrial accidents where the personal factor on the part of the victim is important - are rarely sound in every respect and that in more cases than coincidence could account for, they show a degree of lymphatism.

5. That hyperthyreoidism is definitely associated with lymphatism at all ages.

6. That in hyperplasia of the thymus, Hassall's corpuscles are affected and that these are not therefore to be regarded as merely re-:sidual elements which have lost all active function.

7. That the thymus probably possesses, at least philogenetically and perhaps also during the period of its activity in the human body an "Internal Secretion" which may possibly act in some capacity as a regulator of lympho-:cytes.

REFERENCES
to
LITERATURE IN PART I.

1. Brouardel .. "Death and Sudden Death" Paris, 1894, trans. by Benham.

2. Brown Séquard .. Quot. by 1.

3. McWilliam .. B.M.J. Jan. 5, 1889.

4. Plater .. Quot. by Friedjung Centr. Grenzget. Med. u, Chir. 1900, iii, 465, 523, 587, quot. by 15.

5. Paltauf .. Wien. Klin. Woch. 1889, ii, 877: 1890, iii, 172, quot. by 15.

6. Dudgeon .. Journ. Path. 1904-5,x, 173.

7. Stat. Lymph. Cttee. Journ. Path. 1925, xxviii, 132.

8. Bratton .. Journ. Path. Oct. 1925, xxviii.

9. Cooper .. "Histology of the more im-:portant human endocrine organs at various ages" 1925.

10. Friedleben .. "Physiologie der Thymusdrüse in gesundheit u Krankheit u.s.w. Frankf. 1858.

11. Pool .. Internat. Abst. of Surg. May, 1915, xx, quot. by 9.

12. Fortescue-Brickdale -Lancet, 1905, ii, 1029.

13. McGowan & McNeil .. Journ. Path. xvii, 412.

14. Schäfer .. "Endocrine Organs" 2nd Edit.

15. Marine, Manley and Baumann .. Journ. Exper. Med. 1924, xl. 429.

16. Hammar .. "Morphology of the Thymus" "Endocrinology vol. v. No.v Sept. 1921 and Anat. Hefte vol. xliii, 1911. and anat. Anzeigr xxvii 1905,quot. by 17.

17/

17. Quain's "Embryology" .

18. Spencer .. Lancet, 1897, i.

19. Rolleston .. Journ. Path, 1896, iv, 228.

20. Gulland & Goodall . "The Blood".

21. Hoskins .. Journ. Exper. Zool. 1916, xxi, 295.

22. Hangsted .. "Thymi in Homine ac per seriem Animalium Descriptio" quot. in Lancet, 1896, ii, 1100.

23. Clark .. Lancet, 1896, ii, 1077.

24. Simon .. "A Physiological Essay on the Thymus Gland", 1845.

25. Sonné .. Dict. des Sc. Med. 1887, Sér iii, Tome xvii.

26. Gulland .. Journ. Path. 1894, ii, 447, quotes Zacherow.

27. Waldeyer 1890 .. Quot. by 8.

28. Pepper & Stengel .. Trans. Assoc. Amer. Physic-:ians, 1895, quot. by 19.

29. McCarrison .. "Studies in Deficiency Disease"

30. Emrys-Roberts .. Journ. Path. 1913-14, xviii, 513.

31. Abelous & Billard . Arch. de Physiol. Norm. & Path. 1896, 898, quot. by Myers, Journ. Path, viii, 1902.

32. Ver Eecke .. Quot. by 49.

33. Park & McClure .. Am. Journ. Dis. of Child. 1919, xviii, 317.

34. Van Allen .. Journ. Exper. Med. 1926, xliii.

35. Kastschenko .. Quot. by 49.

36. Weigert .. Neurol. Cent. 1901, xx, 594, quot. by 38.

37. Link .. 1902, quot. by 38.

38./

38. Mendelbaum & Celler .. Journ. Exper.Med.1908,x, 308.

39. Calzolari .. Quot. by 14.

40. Henderson .. Journ. Physiol.1904,xxxi, 222.

41. Goodall .. Journ. Physiol. 1905, xxxii, 191.

42. Herring .. B.M.J. 1920, ii, 886.

43. Paton .. Journ. Physiol, 1911, xlii, 267.

44. Marine & Manley .. Journ. Lab. & Clin. Med. 1917, iii, 48.

45. Klose & Vogt .. Quot. by 14 and Lancet 1910, i, 1,441.

46. Paton .. Journ. Physiol. 1904-5, xxxii, 28.

47. Blair Bell .. B.M.J. 1913, i, 652,707; ii, 1274.

48. Biedl .. "Innere Sekretion" Berl. 1910.

49. Swale Vincent .. "Internal Secretion and the Ductless Glands", 1922.

50. Gudernatch .. Am. J. Anat. 1913-14,xv, 431.

51. Osler & McCrae .. "Principles & Practice of Medicine",10th Edit. 1925, 618.

52. Halsted .. Harvey Lectures, 1913-14

53. McNeil .. Lancet, 1926, i, 980.

54. Harberer .. Med. u. Chir. 1922,xxxii, quot. by 14.

55. Webster .. B.M.J. June 12, 1926.

56. Goodpasture .. Journ. Exper.Med.1921, xxxiv.

57. Kahn .. Arch. f.d. ges. Phys.1916, clxiii, quot. by 14.

58. Owen .. B.M.J. 1895, i, 361.

59./

59. Bücher .. Berl. Klin. Wochnschr. lxxxix 1914.

60. Hoskins .. Endocrinology,iv, 1920.

61, Kopp and Escherich quot. in Allbutt & Rolleston's System of Medicine, Vol.iv. i, 487.

62. Soli .. Quot. by 49.

63. Erb .. Quot. in 61.

64. Cushing .. B.M.J. July 2, 1927, p.i and July 9.

65. Dowd .. Arch. Pediat. 1924, xli, 801.

66. Addison .. "On the Constitutional and Local Effects of Disease of the Suprarenal Capsules 1855.

67. Star .. Lancet, 1895, i, 284.

68. Wiesel .. Internat. Clin. 1905, ii, Ser 15, 288.

69. Schäfer .. Quot. by 49.

70. Crowe & Wislocki .. Bull. Johns Hopkins Hosp. 1914, xxv, 287.

71. Jaffe .. Journ. Exper. Med. xl, 325, 619, 753.

72. Swale Vincent .. Endocrinology, 1917, i, 459.

73. Elliott & Armour .. Journ. Path, 1911, xv.

74. Hewer .. B.M.J. 1922, i, 138.

75. Marine & Baumann .. Amer. Journ. of Physiol. 1922, lix.

76. Dale .. Harvey Lectures, 1921.

77. Lewis .. Amer. Journ. of Physiol. 1923 lxiv.

78. Quot. by Timme B.M.J. Oct. 30, 1926, 771.

79. Beaumont & Dodds .. "Recent Advances in Medicine" Ch. 8.

80. Laignel Lavastine . Paris Méd. 1924, xiv, 593.

81./

81. Buxton .. Lancet, 1910, ii, 365.

82. Rühraḥ .. Lancet, 1903, ii, 602.

83. Duncan .. B.M.J. 1913, i, 1317.

84. Agduhr and Höjer .. Quot. in B.M.J. Feb. 19, 1927.

85. Wallisch .. Quot. by 49.

86. Piney .. "Recent Advances in Haematol-:ogy".

87. Jagic & Schiffner . Wien. Med. Woch. 1920, i, quot. by 86.

88. Beard .. Quot. by 6.

89. Danchakoff .. Journ. Exper. Med. 1916, xxiv.

90. Blumer .. Bull. Johns Hopkins Hosp. 1903, xiv, 270.

91. Hoch .. 1892, quot. by 6.

92. Hun .. Albany Med. Ann. 1904, xxv, 28, quot. by 38.

93. Metchinkoff .. Compar. Path. of Inflamm. Eng. Trans. Pref. p. 8.

94. Hewer .. B.M.J. 1923, i, 235.

95. Leading Article B.M.J. 1910, i.

96. Gallatti & Ohlmacher quot. by 81.

97. Goodall & Rodgers.. B.M.J. June 25, 1927, 1141.

98. Emerson .. B.M.J. 1913, ii, 388.

99. Major .. Lancet, 1922, i.

100. Simpson .. Lancet, 1870.

101. Newbold .. Lancet, March 20, 1926.

102. Adkins, etc. .. Arch. Pediat. 1924, xli, 580.

103. Jackson .. Journ. Amer. Med. Assoc. 1907, xlviii, 1753.

104. Peterson & Miller . Journ. Amer. Med. Assoc. 1924, 234.

105. Morgan, Rolph & Brown .. Journ.Amer.Med.Assoc. March 5, 1927, 703.

PART II.

S Y N O P S I S.

INTRODUCTION .. Post-operative thrombosis and embolism - coagulability of the blood after operations.

METHOD .. Estimation of coagulation-time before and after operations - discussion of details.

RESULTS .. In 80% of cases a shortening of coagulation-time after operation - most marked immediately after - per-:sisting a few hours - not present on the 3rd, 4th and 8th days after oper-:ation - effect of age on the normal coagulation-time and on the post-operative reduction - effect of vari-:ous operations and different anaes-:thetics - the coagulation-time during induction of chloroform and ether, illustrative cases - discussion of the minority which showed no change or increase in coagulation-time after operation - examples - two cases of femoral thrombosis and one of fatal embolism after operations - Cases at the Maternity Hospital.

DISCUSSION Of results with References to Literature - other observers' results with coagulation-time after operations - Reasons for increased liability to thrombosis after operation discussed under the headings:- Mechanical - Physical - Chemical - Acidosis, calcium, effect on jaundice cases - Pharmacological, effect of various anaesthetics, and of morphia - Endocrine, adrenalin, other hormones, the menopause - Biochemical, thrombo-:kinase increased, local and general increase of coagulability, the plate-:lets - Bacteriological, sepsis and thrombosis - a case of pulmonary thrombosis after cataract operation - Seasonal, waves of short coagulation-time in my series - relation of these to the occurrence of thrombosis - Idiopathic, recurrent thromboses -

a/

The work to be described in this paper was under-
:taken at Professor Wilkie's suggestion in order to attempt to discover another and possibly more gener-
:ally applicable cause for that surgical tragedy - post-operative pulmonary embolism.

Increasing attention has been paid to the subject of late years as it seemed to be definitely increasing in frequency of occurrence in spite of all round im-
:provements in surgical technique, and in pre- and post-operative treatment, and many surgeons feel that it ought not to be regarded as an unavoidable accident.

In a recent article on "Unexpected Deaths in the Post-Operative Period" Rendel Short and Fraser[1], con-
:trary to the general opinion, find that this is a rare cause of death after operations - only two cases having occurred in a ten year's series. At the Mayo Clinic it occurred in 1 in 1,200 operations (Heard)[2] - and(Lindsay)[3], summing up the evidence from statistics of various clinics, decides that there is no evidence of increase and quotes Rupp[4] that the incidence of post-operative thrombosis and embolism is only a quart-
:er of that occurring in the course of internal disease without operation.

Opinion is divided as to the main predisposing cause of systemic or pulmonary post-operative thromb-
:osis. There are those who maintain with Cruveilhier[5] that "no sepsis, no thrombosis" is the rule, and others who/

who insist that thrombosis does occur after aseptic operations on aseptic areas such as hernia, cataract, etc., as well as after natural child-birth, and to explain the intravascular clotting they go back to the "marasmic theory" of Virchow[6] - that the blood clots in the vessels owing to stagnation, or else they postulate some actual difference in the blood coagulability after anaesthesia, due perhaps to direct action of the drug on the blood, to loss of fluid from the plasma, to acidosis, etc. in order to account for the phenomenon.

In order to investigate this point - the modification of coagulability of the blood after operations - the following experiments were carried out.

METHOD:

Estimation of coagulation-time of the whole blood has been criticised as a method of studying the coagulability of the blood, but the question of clotting-time comes into the most elaborate methods of estimating the coagulability, e.g., Bloch's[7] or Howell's[8] recalcifying methods, and these also introduce experimental errors in measurements with pipettes, fine dilutions of salt solutions, many changes in temperature, and the deteriorating effects of microbic action on the plasma on standing[9]; and yet it is by the time taken to form a clot as well as by the nature of the coagulum that results are reported; whereas, in a simple method of estimation of the coagulation-time/

coagulation-time, when Addis'[10] three essentials are observed :-

1. Constant known temperature of surround: :ings.
2. Constant amount of contact with the same foreign substances.
3. Clear and definite end-point, always in- :dicating the same degree of coagulat- :ion.

With practice the experimental error may be re- :duced to a minimum.

The instrument used was Gibbs'[11] coagulometer, points of difference from his method being (1) that the platinum wire was heated before each test so that there would always be the same amount of heat in it approximately and (2) that the water-bath during the second set of experiments was kept at 31° instead of 37°C. so that the temperature of the middle layer of water in which the test-tube was immersed with damp air inside it was approximately 30°C.; and the test-tube was always kept in the water-bath until it was applied to the loaded instrument. It was thought by this method to lessen variation in temperature, as the blood must cool to a certain degree in the 10 seconds from the prick till it is immersed in the bath, and then the temperature would have to slowly rise again to 37° . Below 25°, as Dale and Laidlaw[12] showed, the differences of coagulation-time for slight changes in temperature are greater than above it; and the time/

time taken at 30° for each drop to clot - about 3 minutes - was found to be the longest which was con-:venient for routine examinations.

Addis'[10] results on the effect of various temper-:atures on coagulation-time being taken as standard, my preoperative and normal control average at 30° (2 mins. 40 secs.) differ only 5 seconds from his, whereas, from 36 - 40·5°C. he gives 1 min. 25 secs. to 1 min. 30 secs. average, and my average at 37°C. was about 2 mins.

The method of Gibbs'[11] differs from Addis'[10] in the slight but important detail that no ether or alcohol is used in cleaning the skin. The same fing-:er is not used twice to avoid all contamination from clotted blood on the surface.

The same amount of congestion exactly was used in every case, that is, after the prick the distal joint of the finger was quickly flexed by pressure on the nail when a fair-sized drop immediately started out. It was lifted on the loop without allowing it to run down the side of the finger or the loop to touch the skin, and immediately the loaded instrument was pushed into the test-tube and put in the water-bath. The whole process took less than 10 seconds.

Occasionally, difficulty in starting the rolling movement of the drop on the ring, owing probably to agglutination of corpuscles as described by Addis[10], was/

was experienced at the beginning, but the result was not counted unless an easy run of fully one third of the circumference of the ring was soon established, and this movement always stopped abruptly when coagu-:lation occurred; and this was proved to be the same degree of coagulation by immediately shaking off the clot under water in the water-bath.

The preoperative tests were all done on the even-:ing before operation between 7 and 8·30 p.m. immed-:iately after the patients had had a light supper of milk and bread and butter.

The routine "normal" blood pressures were esti-:mated at the same time but as the conditions were not "basal", calculations of the basal metabolic rate by Reads[13] formula gave very irregular results so that it was not worth while comparing them with the coagulation-times.

The post-operative tests were done as soon as possible after the patient was put back in bed before recovery of consciousness, or else within four hours of the end of the operation after the vomiting was over and the patient settled down under heroin. Few patients had any recollection of the post-operative finger-pricks having been made and only a very few felt the slight pain of them. This is important as pain or fear of pain may quite definitely cause short-:ening of coagulation-time. It was noticed with the tests on conscious patients that the first prick often gave/

gave the reading most nearly approaching the average normal (which was always estimated at least once dur-:ing every series of three or four patients) - subse-:quent pricks, especially if the patient were at all nervous or excitable often gave shorter times, all other factors being exactly equal. Also cases which were examined immediately before the operation often showed a shorter coagulation-time than they had had on the previous evening and the pre-operative inject-:ion of atropine (gr.$\frac{1}{100}$), given as a routine 30 min-:utes before operation, could not be responsible as the shortening did not occur in every case.

RESULTS/

RESULTS OF EXPERIMENTS ON COAGULATION-TIME BEFORE AND AFTER OPERATIONS.

There are two series of experiments - one done at 37°C. from 17th Feb. 1926 to 1st Feb. 1927 - the second done at 30°C. from Feb. 1927 to July 1927.

In the first series - at 37°C. - 244 cases ex-:amined before operation - excluding some who were obviously abnormal - the average coagulation-time was 2 mins. 2 secs. 55 cases were examined before and after operation. These had a pre-operative average of 1 min. 59·7 secs. and an average post-operative 1 min. 50·1 secs. - that is an average decrease of 9·6 secs. after operation.

10 cases or 18% showed no change or an increase in coagulation-time after operation; these will be discussed later.

In the second series done at 30°C., 102 cases were examined before and after operation.

Average pre-operative	Coagulation-time	2 mins.	37·6	secs.
Average post-operative	" "	2 "	16·3	"
Average decrease after operations		21·3 secs.		
Average normal	Coagulation-time	2 mins.	39·5	"

22 of these cases or 21·5% showed no change or an increase in coagulation-time after operation.

Of these cases, 20 examined immediately after operation, average decrease 28 seconds; 23 within one/

one hour after operation, sometimes after heroin in-:jection, average decrease 17·4 seconds; 38 cases from 1 - 4 hours after operation, average decrease 16·1 seconds. A few cases (8) examined on the even-:ing of the day of operation, awaking from the first heroin injection and 4 - 8 hours after the end of the operation, average decrease 29 seconds.

24 cases examined on the 3rd day after operation had an average coagulation-time, 2 mins.38 secs. ;

25 cases on the 4th day, average 2 mins. 39 secs. and 44 cases on the 8th day, average 2 mins. 37 secs.

The greatest decrease in coagulation-time was 1 min. 15 secs. in two cases - One, a woman aged 45, radical removal of breast for carcinoma, anaesthetic Chloroform and Ether - per-operative 2 mins. 45 secs., 8 hours after operation, 1 min. 30 secs. The test could only be done once, as patient was conscious and vomiting repeatedly.

The other case, a man of 55, had removal of car-:cinoma of palate done under intra-tracheal ether after induction with chloroform. Pre-operative, 2 mins. 55 secs. - post-operative within one hour, patient stirring, colour rather blue - 1 min. 40 secs. (two tests the same).

The observation was made in the first series that old/

old people and adolescents seemed to have a longer normal coagulation-time than that of adults.

All patients of 60 years and over - the oldest being 84, showed at 37°C. an average coagulation-time of 2 mins. 9 secs. (39 cases). This average did not include a man of 82 with malignant disease of the tongue whose average was 6 mins. 42½ secs., nor another of 65 whose average was 3 mins. 42½ secs. This patient had dilatation of the stomach from chronic duodenal ulcer, but no definite signs of "gastric tetany" were observed.

Of 23 cases of 60 years and over examined in the second series, the average coagulation-time was 2 mins. 34 secs. - slightly below the general average, and these cases showed less decrease of coagulation-time after operation, 14 seconds, four of them showing an increase and one no change.

From four cases under 20 years, the impression had been formed that younger people had a longer coagulation-time. These cases, done at 30°C. showed an average coagulation-time of 2 mins. 48 secs. (general average 2 mins. 37·6 secs, observer's average, 2 mins. 39·5 secs.)

17 cases aged 25 and under - the youngest 13 years - had an average of 2 mins. 31 secs., considerably below the average.

At 37°C. the average was 2 mins. 10 secs. for 31 cases - considerably above the average.

As/

As regards the effect of the operation on young people, the average decrease was 14 seconds, and six cases showed an increase or no change in coagulation-time.

Some explanation may be found in the fact that old and young patients had, on the whole, less serious operations than adults - old people had colostomies for instance, often done under twilight sleep, and the operations on young people included glands in the neck, orthopœdic operations and so on.

The effect of different types of operation on the decrease in coagulation-time was studied.

Operations on aseptic and non-aseptic regions were compared.

Aseptic operations included hernias, goitres, orthopœdic operations, some operations on the test-:icle, operations on malignant glands in the neck - one case of torticollis, etc.

All laparotomies were classed as non-aseptic, only a very few were definitely septic.

ASEPTIC OPERATIONS

Average pre-operative Coagulation-time 2 mins.29 secs.
Average post-operative do. 2 mins.16 secs.
Average decrease - 13 seconds.

NON-ASEPTIC OPERATIONS

Average pre-operative Coagulation-time 2 mins.40·7 secs.
Average post-operative do. 2 " 16 "
Average decrease - 24·7 seconds.

It/

It will be noted that the difference is due, not to the post-operative figures which are the same, but to the pre-operative.

The shortness of coagulation-time among the aseptic cases is largely due to the goitre cases of which the average pre-operative time was 2 mins. 10 secs. (6 cases) and post-operative, 2 mins. 5·8 secs. average decrease - 4·2 seconds. - Average pre-operative time of aseptic cases without goitres, 2 mins. 34·7 secs.

Four cases of radical breast operations were tak-:en separately.

Average pre-operative coagulation-time 2 mins.43·7 secs.
" post- " " " 2 mins. 8·7 "
" decrease - 35 seconds.

This decrease was greater than in any other ser-:ies but was largely due to one case which dropped 75 seconds. Without her the average decrease is 21·7 seconds.

20 gall-bladder cases at 30°C.

Average pre-operative coagulation-time 2 mins.53 secs.
" post- " " " 2 " 29 "

Decrease - 24 seconds.

Both pre- and post-operative times in these cases are longer than average; this is probably largely due to four cases of jaundice having -

Average pre-operative coagulation-time 3 mins.10 secs.
" post- " " " 2 " 42 "

26 gall-bladder cases at 37°C.

Average/

Average pre-operative Coagulation-time 2 mins.13 secs.

14 cases examined pre- and post- showed

Average pre-operative Coagulation-time 2 mins.19 secs.
" post- " " " 1 min. 57 "

Average decrease - 22 seconds.

Of these two jaundiced cases had

Average pre-operative Coagulation-time 2 mins.46 secs.

Of all gall-bladder cases examined, only one show-:ed an increase in coagulation-time after operation of 5 seconds, and two showed no change.

39 cases of laparotomy excluding gall-bladder cases were examined -

Average pre-operative Coagulation-time 2 mins. 34·9 secs.
" post- " " " 2 " 19 secs.

Average decrease - 15·9 seconds.

At 37°C. 27 cases were examined :

Average pre-operative Coagulation-time 1 min. 58 secs.

Average decrease 6 seconds.

12 cases of laparotomy at 30°C. showed no change or increase in Coagulation-time after operation; the greatest increase being 20 seconds.

9 cases at 37°C. showed no decrease - greatest increase was 10 seconds.

In a great majority of cases the anaesthetics used were chloroform and ether.

Two cases were done under local anaesthesia.

A/

A woman of 40 had a small recurrent nodule of carcinoma removed. Her pre-operative time was very long - average 3 mins. 30 secs., post-operative 2 mins. 50 secs. - decrease 40 seconds, 8 hours after operat-:ion.

A woman of 26 had a piece of callus removed from her collar-bone fractured in a street accident - with other injuries-four months before; Pre-operative Coagulation-time 2 mins. 10 secs. - very nervous : Post-operative - just out of theatre - Coagulation-time 2 mins. 30 secs. - Increase 20 seconds.

9 cases were done with scopolamine-morphine anaes-:thesia combined with spinal or local.

Average decrease 3·3 seconds - variable results from decrease of 20 seconds to increase of 25 seconds, two no change.

Four of these were examined while under the drugs before being taken to the theatre; three showed very slight or no change from their normal; one, a man of 72 for prostatectomy, showed a decrease of 27 seconds; he was deeply unconscious, respiration slow and pulse intermittent. (pupils not pin-point.)

Ethyl Chloride was used for induction in 5 cases with an average decrease of 23 seconds after.

One case increased from 2 mins. 15 secs. before to 2 mins. 25 secs. during induction with ethyl chlor-:ide.

Of/

Of two cases examined after ethylene anæsthesia, one decreased 30 seconds - the other 20 seconds in coagulation-time.

14 cases were induced with chloroform, the intra-tracheal catheter passed, and ether and oxygen given.

The average decrease in coagulation-time after operation was 23·2 seconds, two showing no change, one, a goitre, increased after operation from 1 min. 35 secs. average on evening before, to 2 mins, 10 secs. just after operation.

A series of 34 cases were examined during induct-:ion of anæsthesia by chloroform and ether for various operations.

All were examined at least twice during induction - many repeatedly, and the averages of the lowest and highest coagulation-times reached by each patient was calculated in the series.

It was noticed in many cases that the greatest reduction occurred after or during the "excitement stage" and the time often lengthened again when the patient was properly "under" - occasionally a second shortening occurred when the change over to ether was made, and this shortening occurred in every case where manipulations such as introduction of the intra-trach-:eal catheter, or placing the patient in the prone position, etc. allowed a lessening of depth of anaes-:thesia.

Average/

Average pre-operative (Evening before) Coagulation-time for the 34 patients -

2 mins. 33·4 secs.

Average pre-operative (Morning of oper-:ation immediately before starting anæs-:thetic)

2 mins. 30 secs. (14 cases).

Average of lowest Coagulation-time attained during induction by each patient -

2 mins. 8 secs.

Average highest Coagulation-time of each patient -

2 mins. 28 secs.

Average immediately out of theatre or back in bed -

2 mins. 11·5 secs.

The greatest decrease from the pre-operative time was 1 minute; 45 and 30 second decreases being common.

As will be seen by the averages, many patients showed a coagulation-time when at its highest during induction, which was equal to or exceeded slightly the pre-operative normal, but many remained shortened all through induction.

The immediate post-operative reading was reduced in all cases except one - an orthopoedic operation lasting only half an hour where the post-operative ex-:ceeded that of the previous evening by 5 seconds, but in this case the pre-operative morning coagulation-time was 25 seconds longer than that taken the evening be-:fore so that a reduction of 20 seconds did take place during operation./

during operation.

Illustrative cases follow:-

Mrs. J.A. - Aged 38 - Cholecystectomy - Chloroform and ether.

9/5/27 at 7·30p.m.	(no jaundice)	2 mins.	50 secs.
		2 "	45 "
10/5/27 11·38a.m.	just begun C.	2 "	20 "
11·41	excitement, speaking	2 "	5 "
11·45	relaxed	2 "	45 "
11·50	under, ether begun	2 "	25 "
11·53	under	2 "	30 "
12·38	just out of theatre, rather blue and retch-:ing ..	2 "	0 "
12·58	back in bed	2 "	5 "

"P" - Aged 63 - Duodenal ulcer -

6/6/27 8p.m.	.. ..	2 mins.	50 secs.
7/6/27	just before be-:ginning	2 "	45 "
11·28a.m.	after excite-:ment	2 "	15 "
11·31	under	2 "	25 "
12·40	just back in bed.	2 "	10 "

"McC" - Aged 40 - Malignant glands in neck - had tongue operation 2 weeks before.

2/6/27 7·30p.m.	up	2 mins.	15 secs.
		2 "	10 "

(Normal 2 mins. 35 secs.)

3/6/27/

3/6/27 - pre-operative .. 2 mins. 50 secs.
(normal 2 mins. 40 secs.)

11·25a.m.	after excitement	2	mins.	30 secs.
11·30	passing catheter for intra-trach-:eal	2	"	10 "
11·33	failed to pass it under chloro-:form	2	"	40 "
11·36	passing catheter	2	"	15 "
11·40	under chloroform	2	"	30 "
11·43	going into theat-:re - under ether	2	"	20 "
1·15p.m.	just out of theat-:re.	2	"	0 "

22 cases showed no change or an increase in coagulation-time after operation.

7 showed no change, 15 increased, the greatest increase being 35 seconds in a case of goitre which had a coagulation-time of 1 min.35 secs.(average) on the evening before and 2 mins. 10 secs. immediately after operation.

This case is an extreme example of the chief cause of increase instead of decrease after operation - that is abnormality of coagulation-time before operat-:ion. The average pre-operative time of these 22 cases was 2 mins. 21 secs. well below the normal.

Other explanations are suggested.

Five were over 60 years of age, 7 under 25 years,

16/

16 of the 22 were examined 1 - 4 hours after oper-:ation so that an initial decrease in coagulation-time may have been missed.

In four cases scopolamine and morphine was used, in one a local anæsthetic only.

The types of operation are interesting - two were inguinal hernias in men of 23 and 24 years, 4 interval appendix operations at ages 25, 27, 24 and 16 years., a removal of one Hodgkin's gland for examination, drainage of a sinus in an appendix scar (no heroin re-:quired after), a local operation on the clavicle, one chronic osteomyelitis of the tibia; 2 exophthalmic goitres and a diaphragmatic hernia were abnormally short before operations: of these one increased from 2 mins. 15 secs. before and after operation to 3 mins. on the 8th day; another 2 mins. 5 secs. before and after was 2 mins. 20 secs. on the 8th day.

Two were laparotomies for inoperable carcinoma, two were colostomies. Two were drainage of the peri-:toneum after 3 and 4 days of peritonitis from perfor-:ated bowel.

The only case which does not come under any of these headings was a married woman of 30, acute chole-:cystitis, shortly after child-birth - pre-operative 2 mins. 25 secs.: post-operative 2 mins. 25 secs.

Of the first series at 37°C., 5 of the 10 cases showing no decrease were the type of slighter operat-:ions and all except one were examined later than one hour/

hour after operation.

Another, although he underwent a serious short-circuiting operation for tuberculosis of the intestine, showed no fall of blood pressure at the end of the operation and records taken frequently during the oper-:ation showed only a slight fall on one occasion - Time, 1 min. 50 secs. before and after operation.

Another, an unmarried woman of 37 years, was seriously annoyed by having been called "Mrs" (not by the writer) and the pre-operative tests were done while she was still red with wrath. Coagulation-time was very short, 1 min. 25 secs. and continued the same on several examinations and after operation it was the same, 1 min. 25 secs., while on the 10th day when patient was calmly thinking of going home the time was 1 min. 50 secs. (control 2 mins. 0 secs.)

Explanations then of failure to react like the majority by having a decreased coagulation-time after operations come under two heads:-

I. Those who were abnormal before operation.

II. Those whose operation was short and involv-:ed little trauma of tissue.

I. Abnormality before sometimes took the form of lengthened coagulation-time as in cases of inoperable carcinoma or sub-acute obstruction with much pain - possibly/

possibly the adrenals were exhausted (Cannon)[14] and could not react by secretion of adrenalin which short-:ens coagulation-time. These, if relieved at all by the operation, showed a shortening of coagulation-time on the 3rd and 8th days coincident with improvement in their condition. Shortening of coagulation-time must often have been due to excitement especially on the morning of operation and markedly in hyperthyreoidism. These patients often showed a much longer time on the 8th day than at the pre-operative test. Seasonal variations in the normal coagulation-time are discuss-:ed later.

II. The amount of trauma and the time after operation at which the test was done were shown to be factors. The cases which had most actual trauma were probably the radical breast cases, and these show a distinct decrease. Laparotomies probably involve most shock from handling of intestines, etc.; gall-bladder cases are complicated by the fact of their high average pre-operative time and by the fact that many have calcium chloride and sod. citrate injections to avoid haemorrhage, and that, if the jaundice is re-:lieved by the operation, a gradual shortening of coagulation-time follows the operation.

Illustrative examples follow :-

"T.D." - Male 49, Duodenal Ulcer - at 30°C. -

pre-operative/

Pre-operative	..	2 mins. 40 secs.
Post- "	(1½ hours).	2 " 15 "
3rd day	..	3 " 0 "
8th day	..	2 " 40 "

"R.L." - Male 24 - Right inguinal hernia - at 30°C.

Pre-operative (nervous)		2 mins. 25 secs. (N. 2' 45")
Post "	(4 hours)	2 mins. 30 secs.
3rd day		2 " 55 "
8th day		2 " 50 "

Mrs H.H. - 48 - Gall-bladder with jaundice - at 30°C.

Pre-operative	..	3 mins. 15 secs.
Post- "	..	2 " 40 "
3rd day	..	2 " 30 "
8th day	..	2 " 55 "

"W.Y." - Male 45 - Perforated appendix - 4 days ago. - at 30°C.

Pre-operative	(in pain)	3 mins. 0 secs. (N.2'45")
Post- "	(1 hour)	3 mins. 0 "
3rd day		3 " 0 "
8th day -	(much better)	2 " 25 "
10th day	(still improving)	2 " 15 "

During this research two cases of femoral thrombosis occurred and one of fatal pulmonary embolism.

Mrs. M.D. - 49 - Cardiospasm - history of hyperthyreoidism.

14/3/27	Pre-operative ..	2 mins. 30 secs. (N. 2'35")
15/3/27	Post- " within 1 hour	2 mins. 5 secs. (N.2'25")
17/3/27	3rd day	2 mins. 15 "
22/3/27	8th day, variable, average	2 " 25 "
26/3/27	11th day, thrombosis noted left leg ..	
2/5/27	Average of 3 similar tests	1 min. 45 secs. (N.2'30")

7/5/27/

7/5/27 Average of 2 similar results 3 mins.35 secs.
(N.2 " 30 ")

Patient went home two or three days later.

This patient had "white leg" twice before on the left side, once during a puerperium and again when 5 months pregnant.

Mary C. - Aged 23 - Emergency appendix operation 13/6/27 - Patient had been working late as a shop assistant.

13/6/27	- Operation.	
25/6/27	- 12th day - stitches out and that evening thrombosis left leg noted.	
27/6/27	At 30°C.	2 mins.10 secs. (N. 2'55")
30/6/27	No pain in leg	2 mins.10 secs. (N. 2'55")
4/7/27		2 mins.30 secs. 2 " 10 " (N.2'30")
7/7/27	Leg still swollen but feels better	2 mins. 50 secs. (N. 2'45")
8/7/27		3 mins. 0 secs. (N. 2'40")

Mrs. A.W. - Aged 52 - Gastro-enterostomy for duodenal ulcer.

		At 30°C.
23/5/27	- Evening before operation ..	2 mins. 25 secs. 2 " 20 " (N. 2'25")
24/5/27	- Before beginning 11·30 a.m.	2 mins. 0 secs. (N. 2'20")
	11·46 a.m. slight excitement	1 min. 55 secs.
	11·48 a.m. just relaxed	2 " 0 "
	11·51 a.m. lightly under	1 " 45 "
	1·0 p.m. just back in bed	1 " 50 "

A good deal of sickness afternoon and evening - Condition otherwise satisfactory.

29/5/27 - Progressing favourably.

Temperature/

Temperature was 98·8° on 3rd and 5th evenings; otherwise entirely below the line till evening of 1/6/27 when it was again 98·8°, pulse 72 per minute, respirations 20. On 1/6/27 about 9 p.m. complained of numbness in the region of the left hip but went to sleep without difficulty. On 2/6/27 about 1 a.m. woke up complaining of numbness of the whole limb. While nurse was moving the pillow under her knees, she suddenly became pale and pulseless, no complaint of pain in the chest, breathing slow and gasping, slight twitching of left arm and leg, respirations stopped before the heart and she died about half an hour after waking.

Previous History.- One child alive and well, menopause occurred 6 years ago. Formerly considerable dysmenorrhœa for which she was curetted twice and also had an operation for displaced uterus.

Visceroptosis, complete set of false teeth for 12 years. Obviously this patient must have undergone anæsthetisation many times before.

Post-mortem.- 2/6/27.

Well-developed and nourished, no œdema of either leg, lungs slightly œdematous, no sign of infarction.

Upper branch of left pulmonary artery contained a plug of ante-mortem clot apparently embolic. Ante-mortem clot in right auricle.

No clot in inferior vena cava, common iliac veins or/

or femoral veins. In the left internal iliac vein a long mixed clot was found - it was not adherent.

Agonal clots bestrode the bifurcations of the aorta, the left common iliac artery and the innominate artery in the neck.

In the right lung an irregular adherent mass of clot was found at a bifurcation of a medium sized artery running towards the base; behind it was a large dark-red clot and before it fluid blood for 2 cms., then an elongated mixed red and white non-adherent clot.

No primary pulmonary thrombosis in the left lung.

The brain was not examined. Death may have been due to a cerebral embolus - this would account for the twitching of one side.

A short series of 20 cases were examined at the Elsie Inglis Memorial Hospice by the kindness of Dr. Rose.

3 patients at full-term not in labour had coagulation-times 2 mins. 15 secs. - 2 mins. 40 secs. - and 2 mins. 0 secs.

9 patients examined during labour in 1st and 2nd stages had an average coagulation-time of 2 mins. 19 secs.

5 cases examined from ½ to 2 hours after delivery - average/

average coagulation-time 2 mins. 11 secs. - All these cases had light anaesthesia during the later part of the second stage.

1 case examined 18 hours after a long labour - coagulation-time 2 mins. 30 secs.

1 case on the 7th day of the puerperium with no complications - Coagulation-time, 2 mins. 0 secs.

It should be mentioned that this case with two others was examined on 25/5/27 during one of the waves of low coagulation-time; and all were very short - but if they are omitted the average coagulation-time of those immediately after labour comes to 2 mins. 18 secs.

The number of the pregnancy did not affect the shortening, multiparas being similar to primiparas.

DISCUSSION OF RESULTS WITH REFERENCES TO LITERATURE.

It is assumed by many writers that intravascular clotting may be expected to occur more readily after operations, and thrombosis of veins in various parts of the body has been suggested as a cause for post-oper-:ative parotitis, (Silbermann and Kagan)[15], haematemes-:is or dilatation of the stomach from embolism in the gastric veins (Von Eiselsberg)[16] and (Lockhart-Mummery),[17] and post-operative pulmonary complications to small infarcts (De Quervain)[18], or primary thrombosis in the pulmonary vessels (Glynn and Knowles)[19].

Mennell and Dudgeon[20] tried to ascertain whether any shortening of coagulation-time occurred after operations - they thought there was, but the research was not pursued.

Adler and Keller[21] obtained negative results, and Chanvin and Esmenard[22] who used the "drop on the slide method" reported that "alterations in the coagulation-time of the blood as a result of operative interfer-:ence are of little significance -- more often than not a slight increase in coagulability was observed (17 times out of 25)".

Straus and Rubin[23] in a recent article report on the effect of ethylene anaethesia on the coagulation-time of the blood.

They noted that in practically every instance coagulation-/

coagulation-time was shortened during the administrat-:ion of the anaesthetic by ½ - 3 minutes and a further drop was noted at the termination of anaesthesia. On the day following operation the coagulation-time increased, often returning to that noted before.

Many reasons for the increased liability to thrombosis after operations under anaesthesia have been suggested - they are mechanical, physical, chemi-:cal, biochemical, pharmacological, bacteriological, endocrine, psychic and climatic, but most writers are careful to state that, while the presence of one or more of these factors seems to predispose to clotting, the actual cause is still unknown.

The mechanical factor is certainly of importance although stasis of blood alone does not cause clotting, as proved by Hunter[24] in his"living test-tube" experi-:ment on a ligatured vein.

It may account for the localization of thrombosis, 42% according to Lindsay[3] occurring in the veins of the pelvis and lower extremity, 50% in the left iliac or left common iliac veins. The mechanical factor is probably of great importance in cases of primary pul-:monary thrombosis, which is believed to be a common condition (Bristowe)[25](Pitt)[26](Box)[27]. Professors Glynn and Blair Bell[28] claim that the recognition of the possibility of this condition and prophylaxis on mechanical/

mechanical lines to prevent pulmonary stasis has considerably lowered its incidence in gynecological cases.

It is interesting in this connection to note that the sequelae of pulmonary infarction, when the emboli are not large enough to kill the patient outright, depend to a large extent on the mechanical condition in the lungs, proved experimentally by Karsner,[29] and Glynn[19] showed that the oldest parts of the autochthonous thrombi where organisation had begun were found in the dependant congested lower lobes.

Marantic thrombi, (Virchow)[6], occur in patients whose blood pressure and circulation rate are low because of age or cachexia, heart or kidney disease, and the increase in the condition in post-operative cases is by many supposed to be due to the higher age limit of operable cases nowadays.

Pre-operative morphia and the repetition of sedatives soon after recovery from anæsthesia by depressing muscular activity and especially respiration; and the reflex inhibition of diaphragmatic movement after abdominal operations must certainly contribute to the condition of stasis in veins (Pasteur)[70].

The frequency of thrombosis in gynecological and abdominal cases, especially gall-bladders, is supposed to be due to the posture of these patients on the table (Gordon-Watson, etc.)[30].

Cowell[31]/

Cowell[31] has shown that a distinct fall of blood pressure follows the change from dorsal to lateral position after abdominal section.

Jeans[28] thinks that phlegmatic patients who lie still are more liable to thrombosis and that it is rare in excitable patients.

Wheeler[32] remarks that the condition occurs more often in private patients who are kept in bed longer and with less excitement than in hospital wards.

Glynn[19] notes that the fatalities often occur on awaking from sleep which by physiological lowering of vital activities perhaps accelerates thrombosis.

The lowering of general blood pressure after operations may be due to the anæsthetic, or to the effect of chloroform combined with trauma to tissue liberating histamine (Dale)[33]; or to psychic influenc-:es, fear (Buxton)[34], acting through the splanchnic nerves on the suprarenals and stimulating the secret-:ion of a quantity of adrenalin within the range of doses which have a depressor effect on blood pressure as shown by Elliott[35]. The loss of tone and move-:ment of voluntary muscles in histamine shock will accentuate the tendency to peripheral stagnation[33].

The <u>physical</u> condition of the blood after oper-:ations might be altered in the direction of an in-:crease in viscosity. Loss of fluids from the body by pre-operative purgation and starvation, and pre- or post-/

post-operative vomiting, diarrhoea or haemorrhage, would all tend to concentration of the blood.

These changes were observed by Keith and Robert-:son[36] in measuring blood volume by the vital red method.

Sherrington and Monkton[37] found the specific gravity increased in the blood in shock; and Cannon and Fraser[38] found concentration of both systemic and capillary blood.

These observations were made on cases of wound shock during the war, which is, as Cowell[31] points out, exactly similar to surgical shock occurring after prolonged operations under chloroform especially.

It is to be noted, however, that thrombosis and pulmonary embolism was almost unknown during the War, in spite of the presence of all these predisposing causes and also that children who succumb readily to shock seldom, if ever, get thrombosis even after burn-:ing injuries, and also that thrombosis occurs after very slight, short operations where the shock element has given no anxiety and there has been no haemorrhage or handling of intestines etc. to account for it.

Dale and Laidlaw[33] draw the conclusion that "the leakage of plasma from the vessels into the tissues, with the reduction in the volume and increase in the viscosity of the blood which it entails cannot be the main cause of the shock, though it doubtless accentu-:ates/

accentuates its severity. The characteristic feat-:ures of the condition are due not so much to the fact that the volume of blood is reduced as to the tendency of what remains to stagnate at the periphery in the capillaries and venules instead of returning to the heart".

Another physical change in the blood which would tend to increase its viscosity is fat embolism in the pulmonary circulation. This, according to Sutton[39], was a very common occurrence after wounds or operations involving fatty bone marrow, brain, liver, omentum or subcutaneous tissue, when fluid fat could get into the proximal end of injured veins. In my series of acci-:dent cases and others in Part I., fat embolism in the capillaries of the lung was looked for microscopically but only found in one, case XLV, where there was serious injury to the chest. Sutton[39] points out the relat-:ionship of venous lipaemia to lowered arterial blood pressure, and to slowing of the pulmonary circulation causing decreased aeration of the blood and so produc-:ing acidosis.

This introduces the next factor - the <u>chemical</u> which is interrelated with both the previous ones.

The tension of carbon dioxide in the blood is an important factor in determining the onset of thrombos-:is after an injection of nucleo-protein (Wright)[40], (Welsh)[41] and in the localisation of the intravascular clot/

clot in the right heart and pulmonary artery in heart disease and in pneumonia, or in a tetanized limb (Wright)[40], and it would also explain the frequency of primary pulmonary thrombosis (Glynn)[28].

A definite lowering of the alkaline reserve of the blood occurs during anæsthesia even when it is of extremely short duration - the larger part of the fall occurring during the first few minutes of anæs-:thesia (Cullen)[42] etc. quoted by Potter[43] who proved on two patients as controls that the fall was not due to the preliminary treatment by purgation, starvation, morphia and atropine injections, etc., in one of these controls the reserve being even increased.

During well-given anaesthesia there should be no asphyxia, and the hyperglycæmia which occurs in as-:phyxia, along with increased viscosity and shortened coagulation-time (Cannon)[14], and which is observed regu-:larly during and also after anæsthetics (Pemberton and Cunningham)[44] and was supposed to be due either to the excitement of induction or to asphyxia, might also be due to the ether itself (Ross and McGuigan)[45] or to the preliminary injection of morphia where that is used as a routine. That the increase of sugar in the blood has no effect on coagulation-time was shown by Cannon[14].

Infusions of glucose subcutaneously or intra-:venously 5-15% solution have even been advised as anti/

anti-coagulant (De Quervain)[46].

Cyanosis either during induction or during recov-:ery from anæsthesia due to efforts at vomiting or falling of the jaw, etc. was found in several cases to shorten the coagulation-time markedly in my series.

Alterations in the calcium content of the blood have been assumed to be of importance in modifying its coagulability and an increase of calcium was expected to cause a liability to intravascular clotting.

In some bone diseases, it has been observed (Wallis)[47] that the blood coagulates very rapidly even when three times the usual amount of sodium citrate is added.

It is interesting to note that in tetania para-:thyreopriva there is no lengthening of the coagulation-time (Simpson and Rasmussen)[48].

The frequency of thrombosis after typhoid fever was supposed by Wright[40] to be due to the prolonged dietery of milk, and Hutchison[49] has assumed that an exclusive diet of milk before and after operations might predispose to thrombosis, and other workers have given lemon juice in order to counteract it. Para-:thyreoid has been given with the same idea of increas-:ing calcium content and so shortening coagulation-time in cases of menstrual menorrhagia (Allen, etc.)[50].

Probably, however, the blood contains the optimum amount of calcium necessary to allow the ferments to act and the addition of more calcium might tend to re-:duce the clotting capacity rather than to increase it (Lockhart Mummery)[17]./

(Lockhart Mummery)[17].

Addis[51] definitely showed that the administration of calcium or citric acid by the mouth had no appreci-:able effect on the coagulation-time of the blood, and Gibbs[11] obtained completely negative results with calc-:ium chloride intravenously, 20 c.c. of a 1% solution.

Barlow and Ellis[52] noted in one of their cats after double suprarenalectomy that the calcium content of the blood was more than doubled, in association with diminished coagulation-time.

(Two injections of calcium chloride intravenously were given on the two nights before operation and an intramuscular injection of sodium citrate on the morn-:ing of the operation to patients who were jaundiced. One, a woman of 63 had her coagulation-time brought down from 2 mins. 30 secs. at 37°C. to 2 mins. 15 secs. on the evening before operation, 24 hours after the first calcium injection, and it was further reduced to 2 minutes after the operation.

In another, a woman of 36, jaundiced for 5 weeks, the time had increased by 15 seconds at 30°C. on the morning of the operation and she showed very little shortening during induction or after the operation.)

Wallis[47] noted that the blood in alcoholism clots very readily and Briggs[53] refers to a case of recurrent thrombosis with very short coagulation-time depending on the presence of fluorine in the beer drunk by the patient.

The/

The pharmacological aspect of post-operative blood changes has been rightly considered of great importance, and the anaesthetic drugs have had their share of blame in the causation of thrombosis. It is a common observation of laboratory workers that the blood of experimental animals taken after anaesthesia, clots better, i.e. leaves a clearer serum, and much quicker than that of unanaesthetised animals, so that specimens taken under the former conditions may be ex-:amined the same day instead of being left over-night to complete the contraction of the clot. (personal communication Miss J. McCallum, B.Sc. Aberdeen).

Multzer[54] showed in experiments that there is an appearance of intravital coagulation in the vessels in the internal organs after ether and chloroform.

That chloroform causes haemolysis in vitro more readily than does ether is noted by Prof. Blair Bell[28]. Ether is one of the many substances which, when inject-:ed intravenously, causes intravascular clotting (Naunyn),[41] and Straus and Rubin[23] suggested that the shortening of coagulation and bleeding times which they obtained might be due to direct action of ethylene gas on the red blood corpuscles.

That the specific gravity of the blood of healthy animals is increased after operations under inhalation anaesthesia by various drugs was shown by Sherrington and Copeman[55].

Buckmaster[56] said that the drug entered into loose/

loose combination with red blood corpuscles, displac-:ing some oxygen, and this anoxaemia alone might cause lowering of the alkaline reserve (Potter)[43].

The most important action of anæsthetics on the blood coagulability is probably an indirect one through stimulation of the adrenals through the splanchnic nerves and outpouring of adrenalin (Elliott)[35], but Bedford[57] noted that anæsthetisation and general oper-:ative procedure did not bring about increase of ad-:renalin in the blood; this was only obtained after prolonged shock conditions.

That increase of adrenalin in the blood does cause a shortening of coagulation-time will be dis-:cussed in a succeeding paragraph, but it may be well to mention here that observers disagree as to the effects of ether and other drugs on the coagulation-time. Mendenhall[58] found that ether hastens coagu-:lation in decerebrated cats; Gray[59] on opossums and Barlow and Ellis[52] on cats obtained an increase of coagulation-time 6 - 24 hours after operation rather than a decrease. Falls[60] noted no difference with ether on women in labour.

Straus and Rubin[23] observed shortening in coagu-:lation-time after ethylene; Chauvin and Esmenard[22] state that the variations they obtained "bear no re-:lation to the anæsthetic employed" just as marked variations after local as after ether or intraspinal anaesthenia.

Thrombosis/

Thrombosis and embolism have occurred after local anaesthetics, such as cocaine and adrenalin for cataract operations (Parry[61] and Cresswell)[62].

It is interesting to note in this connection that Von den Velden[63] observed that the coagulation-time is decreased after the nasal mucosa has been rendered anaemic by adrenalin pledgets.

The effect of most anaesthetics in deepening shock is well known - Dale and Laidlaw[33] have shown that quantities of histamine, too small to produce any effect upon a normal animal, cause a marked fall of blood pressure when injected into an animal after prolonged chloroform anaesthesia.

The injection of morphia often given as a pre-operative routine (but not in the cases I examined) might have an effect on coagulability. Morphia causes hyper-glycæmia, and in cats, when it produces all the symptoms of fright, it causes secretion of adrenalin (Elliott)[35]. The effects of scopolamine-morphine anaesthesia were noted in nine cases.

Chemical and pharmacological considerations lead on to the subject of <u>hormones</u> - the chemical substances produced by the body itself and acting through the blood on various tissues and organs after the manner of a drug - the autacoids (Schäfer)[64].

Adrenalin increases the coagulability of the blood (Schäfer)[64] and injections of adrenalin are followed, in normal persons, by a thrombocytosis (Piney)[65]/

(Piney)[65] quoting Schenk. Vosburgh and Richards[66] first noted more rapid coagulation to occur simultaneously with the increase of blood sugar after administering adrenalin, the diminution in clotting time being as much as $\frac{4}{5}$ of the control. Wiggers[67] found "never the slightest indication that adrenalin, either when injected or added to blood appreciably hastened the coagulative process".

Von den Velden[63] affirmed that adrenalin decreases coagulation-time of blood <u>in vitro</u> but believed its effect in the body to be due to vasoconstriction disturbing the normal equilibrium between the blood and tissues.

Cannon and Gray[14] found rapid clotting was manifest directly after minute doses of adrenalin intravenously, or after ten times as much subcutaneously.

Cannon[14] also showed that the hastening of coagulation-time was not due to direct action on the blood, nor to vaso-constriction, but that it acted through some organ in the abdomen, probably the liver as ligature of its vessels or phosphorus poisoning result in a great lengthening of clotting time.

Stimulation of the splanchnic nerves produced the same result as injection of adrenalin and stimulation of the nerves of liver and intestines with the adrenals removed caused no shortening and sometimes a lengthening of coagulation-time.

Now/

Now, during an operation under anæsthesia there are several conditions produced at various times which, by calling forth adrenalin in minute doses, would cause increased coagulability of the blood. These are -

1. Fear or excitement before, or during the excitement stage of induction.

2. Operative procedures under light anæsthesia or reduction of anaesthesia soon after operation.

3. Asphyxia - Cannon[14] proved all three in his experiments on cats, and I have frequently ob-:served this shortening during induction of anæsthes-:ia which disappears when the patient is fully under - to return again during introduction of the intra-trach-:eal catheter or changing the position of the patient, involving a lightening of anæsthesia.

4. The action of the anæsthetic, chloroform or ether, in discharging adrenalin from the suprarenals (Elliott)[35].

5. Low blood pressure and shock cause increase of epinephrin to be thrown into the blood. Bedford,[57] this worker noted difficulty with coagulation of the blood preventing free flow of blood in the adrenal veins after and during the production of shock.

Cramer[68] also in experiments on mice showed that severe uncomplicated haemorrhage causes active secret-:ion/

secretion of adrenalin and depletes the medullary cells, whereas in post-operative shock the cells are still fully charged, showing that death in shock is not due to exhaustion of the adrenals.

The effect of other endocrines is probably exert-:ed through the adrenals. The coagulability of the blood is decreased in cretines (Schäfer)[64] and there is some evidence that it is increased in hyperthyreoid-:ism in my cases, although two of the cases, classed as goitres, had no increase in basal metabolic rate but had very short coagulation-times before operation - the state of "crystallized fright" (Graham - Brown) in which exophthalmic goitre cases live might be supp-:osed to keep their coagulation-time low, but thrombos-:is after goitre operations is rare (Wheeler)[32].

If some of the symptoms of the menopause, such as flushings, are due to over-sensitiveness to adrenalin in the blood as Hannan[69] believes, this might alter the coagulability of the blood, so that these patients would be more liable to thrombosis and might account for the fact that in many clinics the incidence of thrombosis is greatest among gynecological operations.

Parathyreoid extracts and calcium metabolism have been discussed.

In order that coagulation of blood may take place, certain factors must be present - fibrinogen, thrombo-:gen/

thrombogen, calcium ions and thrombo-kinase. The possible alterations in biochemical constitution of the blood after operations will now be discussed.

In any operation thrombokinase must be liberated from the wounded tissues and may give rise to (1) local thrombosis (2) a general increased liability of the blood to clot.

(1) Thrombosis near the site of operation is an important and easily comprehensible cause of post-operative pulmonary embolism, especially after oper-:ations where large veins are traumatised by stripping or clamping or where a mild sepsis of the wound initi-:ates a spreading thrombosis.

Another type of thrombus - the so-called hyaline thrombi due to agglutination of red blood corpuscles in capillaries, arteries or veins - occurs especially in general or local toxæmias and may be of importance in some post-operative cases. This may also be due to the action of the anaesthetic on red blood corpusc-:les (Mulzer)[54].

Local thrombosis probably sufficiently explains puerperal cases and those after gynecological or vari-:cose vein operations and some abdominal operations from injury to the epigastric veins, but other factors must be called in to explain "crossed" thrombosis (as "white leg" on the left side after appendectomy in the case of Mary C.) or pulmonary thrombosis in the medium sized/

sized branches in both lungs which could not possibly be due to embolism (Glynn)[28].

Also thrombosis is rather rare in breast cases who are often about fifty, and have secondary anaemia, often slight infection of the skin brought together under tension, large veins are freely exposed and manipulated (Wheeler)[32], and chest movements must often be hampered by large dressings (Wrigley)[71].

(2) Some local thrombosis must occur after all operations, and blood, in which thrombosis is occurring, is rich in thrombokinase - nucleo-proteins are also liberated from the wounded tissues and so alter the coagulability of the blood that it begins to clot in vessels where there is stasis, or a churning movement - where tributaries join large veins, or excess of carb-:on dioxide in the dependant parts of the lungs (Glynn)[19] (seen in the case of Mrs A.W. as well as a very general tendency to intravascular clotting).

Wooldridge[41] has shown that thromboses are partic-:ularly prone to occur in the portal system after the injection of substances favouring coagulation, but, of course, there is no danger of embolism to the lungs from these veins owing to the sieving action of the liver.

Neither venous stasis alone, then, nor thrombo-kinase from the wound without stasis asphyxia or other adjuvants is sufficient to account for thrombosis, but it/

it is obvious that clotting will begin when all these factors are at a maximum, that is, either during or very soon after the operation; and this accounts for the fact that, although the commonest time for pul-:monary complications to follow thrombosis is during the second week, when movements are freer, and a piece of clot, being in a friable stage, may become detached, still fatal pulmonary embolism has occurred within 24 hours of the operation.

There appears to be no definite and constant re-:lation between the amount of fibrin obtainable from the blood, or the rapidity of its coagulation in the test-tube and the occurrence of thrombosis in human beings (Welch)[41]. It would seem then to be extremely difficult to find a method of measuring the coagulabil-:ity of the blood because the very withdrawal of it from the vessels introduces factors which are not pres-:ent in the condition of circulation.

Under the heading of biochemistry one might dis-:cuss the morphological changes in the blood especial-:ly variations in the numbers of platelets as these elements are supposed to be the chief producers of the ferments involved in coagulation. Methods of enumer-:ating these bodies are at least as difficult and as productive of gross experimental error as the measure-:ments of coagulation-time (Cramer, Drew,[72] etc.) but several interesting facts have been noticed which may have/

have a bearing on post-operative thrombosis.

There is an increase of platelets after haemorr-:hage and in secondary anaemias, such as occur in cases of malignant disease, and are sometimes assoc-:iated with systemic thrombosis; they are also in-:creased at the end of pregnancy and after delivery (Cadet, Hayem, Welch)[41].

The increase of platelets after adrenalin inject-:ion has already been referred to.

In histamine shock and other similar conditions associated with stagnation of capillary flow, plate-:lets appear in increased numbers and are often in clumps (Dale)[33].

The question of the presence of organisms or their toxins in the blood in thrombosis or rather of the possibility of clotting without sepsis has long been in dispute.

Hunter and Cruveilhier[41] regarded thrombosis only as an expression of inflammation of the inner lining of the vessels - the material composing the thrombus being an exudate of coagulable lymph from the inflam-:ed vascular wall. Virchow[6] in 1846 in his monument-:al work on thrombosis,(Welch)[41] reversed the order, saying that the inflammation of the wall, if present, was a secondary effect of the thrombus which was the result of great prostration alone. Serious objections were/

were later raised to this theory because "marantic thrombi" were often found to contain organisms.

There is no doubt that in certain bacterial in-:fections, such as pneumonia and typhoid, the coagu-:lability of the blood is much altered and thromboses occur during the "positive" phase.

Owen[73] notes that in influenza epidemics accid-:ental hæmorrhage in pregnant women (due to infarct-:ion of the placenta) along with pulmonary infarction is common, and he supposes that both are due to a tendency to thrombosis in this infection.

Addis, quoted by Gulland[74], states that only when the organisms are actually in the blood is the coagu-:lation-time altered.

Loeb[75] is of opinion that the alteration is due to chemical, not physical, properties of the bodies of the bacteria.

This being so, one would expect peripheral thromb-:oses to occur most frequently in septic cases, for in addition to the presence of organisms, the patient lies as still as possible and gets frequent sedatives, a septic wound being so much more painful than one healing by first intention, and yet thrombosis in the general circulation is distinctly rare in these cases and was almost unknown in the War and seldom occurs after accidents. Welch[41] remarks on the frequency of latent thrombosis preceding fatal pulmonary embolism in/

in the larger statistics, the temperature chart show-:ing no indication of septic mischief.

Beneke[76], however, was able to culture organisms from thrombi in 80% of cases and the same organisms were sometimes found in blood culture, and even if organisms are not obtained, he states that they may have disappeared after setting up the lesion - as in some vegetations on the heart valves.

Against the septic theory of origin of pulmonary embolism is the fact that if not immediately fatal the infarction is bland - the temperature being due to ab-:sorption of blood from the infarcted area as in hæmo-:thorax (Latham)[17]- or is followed by a pneumococcal consolidation rather than the septic infarct, which should be produced by an embolus carrying organisms.

Another great difficulty is that embolism may occur at any time from the hour of operation, before the septic process could have incubated.

Blair Bell's[28] opinion is that major sepsis at the site of operation (gynecological) may give rise to a spreading thrombosis which may be followed by pulmon-:ary embolism, whereas minor sepsis gives rise to a mild degree of toxæmia which, with other factors, such as stasis and poor oxygenation in the convales-:cent state, gives rise to the "much commoner condit-:ion" of primary pulmonary thrombosis, assisted locally by septic conditions of the air-passages following the anaesthetic, inhalation of stomach contents, etc.(Glynn)[28].

Others/

Others, on the contrary, think that massive em-:bolism is due to stasis and is non-septic, while small infarcts are due to broken down clot and mild sepsis (Gordon-Watson)[3].

The occurrence of fatal pulmonary embolism after operations under local anæsthesia for removal of cat-:aract is extremely difficult to explain by the septic or indeed by any other theory - the patients are elder-:ly, often depressed, and are kept in bed a few days.

Such a case was Miss H.L., aged 73 - P.M. 133 - 15/3/27 - who died about four weeks after cataract operation under local anæsthesia. She had been up for a few days when she developed a slight cough with slight temperature but no pain in the chest - signs of consolidation at both bases, and later fairly copious, blood-stained sputum "suggestive of infarct". She got gradually weaker but died quite suddenly.

At the post-mortem there was adherent clot partial-:ly blocking the right pulmonary artery, rather curled up and with its tail mixed with post-mortem clot. No thrombosis was found on the left side but the consolid-:ation at both bases was found microscopically to be due to infarction.

No ante-mortem clot was found in the heart nor in the systemic veins.

Certain writers have remarked that post-operative embolisms occur in small epidemics (De Snoo),[77] and might/

might almost be said to have a seasonal incidence (De Quervain)[46] with a maximum in February and March, June and October. This has been used as a strong argument in favour of their bacterial origin, certain "thrombosis cocci"[77] being inculpated and the cases isolated especially in maternity wards as septic - as many of them undoubtedly are.

It has been observed, however, that sudden deaths of all kinds, especially in circulatory cases are "epidemic" and high barometric pressure[78], sun-spots[79], etc. have accounted for this to some people.

Might it not be possible as Fayrer[80] suggested, that life in some climates predisposes to thrombosis. The ancients may have had an element of truth in their belief that the stars cast an influence on the bodily humours, especially the blood. Another suggestion is that at certain periods of the year less of the essent-:ial food factors are present in food - one physiolo-:gist quoted by Lindsay[3] believed that increase in the incidence of thrombosis might be due to American bacon and Chinese eggs ! Avitaminosis would probably act through the suprarenal as the adrenalin content of the gland is measurably increased in this condition (Syden-:stricker)[81], etc.

I have noticed during routine examination of coagulation-time that there are certain days when all pre-operative times are short and when the normal con-:trol is also reduced - the greatest care being taken of course/

of course to eliminate all other causes of such variat-:ion, such as a dirty loop or too hot water.

For instance, on 17/3/27 the average of 5 tests was 2 mins. 22 secs, normal, 2 mins. 30 secs. On 21/3/27, average of 7 tests on four patients - 2 mins. 6 secs., normal 2 mins. 20 secs. On 22/3/27 all these patients showed an increase in coagulation-time after operation, done within 4 hours, average 2 mins. 18 secs., normal, 2 mins. 25 secs.

Mrs M.D. who was at her 3rd day post-operation on 17/3/27 had a coagulation-time of 2 mins. 15 secs.

(Note also that on 15/3/27 the cataract case died.)

On 23/5/27 another wave of low coagulation-times occurred; three tests on two patients gave an average of 2 mins. 20 secs., normal, 2 mins. 25 secs. - next day both showed great reduction during anaesthesia with an average post-operative time of 1 min. 48 secs. normal, 2 mins. 20 secs. One of these patients was Mrs. A.W. who died on the 9th day of embolism.

On the date of 13/6/27 on which Mary C., the 3rd case showing thrombosis, had her operation, the average of six tests was 2 mins. 37 secs., normal, 2 mins.50 secs. and no wave of short times occurred till after the thrombosis declared itself on 25/6/27. On 30/6/27 5 tests gave an average coagulation-time of 2 mins. 11 secs., but this time the normal was not affected, being 2 mins. 55 secs.

All/

All other factors being apparently the same, one has to call in personal idiosyncrasy to explain why some people's blood will clot while others' does not, and to account for cases of recurrent thrombosis al-:though, of course, mechanical injury to the vein wall during an attack of thrombosis must predispose to clott-:ing in that situation again. Gounet, etc.[82] report a case of a woman who had had white leg in each of her eight confinements, but after treatment with leeches she showed no thrombosis in her 9th.

Perhaps some people have a definitely shorter coagulation-time than others - it was noted in the few cases who were examined twice in health after a lapse of weeks or months between two operations that the pre-operative time was usually identical though the react-:ion to operation was different in one case as follows -

J.M. - Male aged 63, carcinoma pelvic colon.

17/2/27	- pre-operative	2 mins. 25 secs.(normal, 3 mins. 0 secs.)
18/2/27	- 1 - 4 hours after oper-:ation ..	2 mins. 45 secs.
21/2/27	- 4th day ..	2 mins. 45 secs.
25/2/27	- 8th day ..	2 mins. 20 secs.
7/7/27	- readmitted for excision of tumour -	(Normal, 2 mins. 45 secs.)
	pre-operative	2 mins. 25 secs.
8/7/27	just back in bed.	2 mins. 0 secs.

The profound metabolic changes which occur in pregnancy and the puerperium may have effect on the coagulability/

coagulability of the blood so that if some of the other factors, such as sepsis, be present, thrombosis readily occurs. The number of blood platelets is said to be increased in the later months of pregnancy and in the puerperium (Welch)[41] and(Pruvost)[83] and hyper-coagulability with hyper-retractility of the clot has been observed. Falls[60] in a study of coagu-:lation-time before and after labour found that fig-:ures before and after delivery were "well within norm-:al limits", while "blood taken during labour, just before the birth of the baby, coagulates a little more quickly". Meyer Solis Cohen[84], however, found that menstruation and pregnancy caused no change in coagu-:lation and the puerperium decreased the coagulability slightly. Pfeiffer and Hoff[85] found a well-marked reduction in the number of platelets in menstruation, which fall may reach as low as $\frac{1}{3}$ of the normal, and occurs immediately the flow starts.

I have not noticed any increase in coagulation-time during menstruation in normal people.

Short coagulation-times were noted in a short series of pregnant and parturient women.

The psychic upset before and after operations is very considerable in most people and this must have an effect on the coagulability of the blood on which anger, fear, and other intense emotions can produce measurable changes/

changes even in lower animals (Cannon)[14](on cats).

Cowell[31] showed that soldiers who had been long exposed to the excitements and fatigue of battle, succumbed more easily to shock and after less severe injuries than did those who were wounded while they were fresh.

Wheeler[32] compares the whole subject of post-operative thrombosis to the Riddle of the Sphynx, and certainly when one considers all the possible factors at work, one is led to believe that there is no single solution of the problem which could fit every case. This increases the difficulty of discussing <u>prevention and treatment</u>.

Study of the treatment of an attack of pulmonary embolism is not of great importance, because patients who survive ten minutes usually recover in any case, whereas massive embolism is so rapidly fatal that no treatment is of any avail. Trendelenburg's oper-:ation of embolectomy has not been successful.

Morphia may relieve pain and anxiety, which are great in all these cases, and oxygen has been shown experimentally to relieve the cyanosis and rapid shall-:ow breathing in animals after pulmonary embolism was produced (Binger,etc.)[86].

Amyl nitrite has been advised to lessen the work of the heart and bleeding recommended to ease the venous pressure on the right side of the heart, and atropine/

atropine to paralyze the vagi whose reflex stimulation has been shown by Dunn[87] to be the initial cause of the dyspnœa. Strychnine and other stimulants are said to be useless and even harmful (Lockhart-Mummery)[17]. If the patient survive, treatment of the pleuritic pain will be necessary. It has been shown experi-:mentally[29] that consolidation is much more likely to occur after embolism in previously diseased or passive-:ly congested lungs. If associated phlebitis becomes obvious, absolute rest is indicated for 8 - 15 days (De Quervain)[46], as recurrent attacks of bland or grave embolism are to be feared (Wharton and Pierson)[88] Operative interference with the thrombosed vein is not advised.[46]

Medical treatment, that is, the injection of subs-:tances to alter the coagulability of the blood, has not met with much support on account of the extreme difficulty of adjusting their action so as to check a spreading thrombosis without making a clot, already formed, more friable, or in prophylaxis to steer be-:tween insufficient hæmostasis on the one hand and intravascular clotting on the other. The application of leeches to the "white leg" has been practised by Gounet[82], etc., who attribute good results to the gener-:al anti-coagulant effect on the circulating blood. They do not claim that clots already formed are diss-:olved but that they are prevented from propagating themselves.

Another/

Another safe anti-coagulant would be intravenous glucose injections[46] which would also tend to supply energy to heart muscle and prevent pulmonary and sys-:temic stasis. All surgeons are of the opinion that prevention is the only satisfactory course of treat-:ment.

All the mechanical and physical factors which would tend to increase the coagulability of the blood, are to be avoided in pre- and post-operative treatment and asepsis both of the wound and of the air-passages is to be aimed at. It was a remarkable fact that the lungs of cases dying suddenly within a few hours of operations, examined in the first part of my research, all showed evidence of inhalation of stomach contents and a broncho-pneumonia was commencing in Cases XXXVI and XXXVII. Such local lung infections must predis-:pose to pulmonary thrombosis (Glynn)[28].

Breathing exercises immediately after operation in gynecological operations are highly recommended by Blair Bell[28]; other surgeons believe in early move-:ments of the limbs - massage is not advisable, even soon after operation, because of the danger of moving a clot already formed[46].

De Quervain's[46] counsel of dispair is to rejuv-:enate the older patients or else to get them to come to operation earlier in life, but it appears that middle-aged patients are in more danger from this com-:plication than the aged. It is also noted that older people/

people, in whom thrombosis is for other reasons to be expected, have blood whose coagulability is often less than that of adults before operation and which appears to be less affected by operation.

CONCLUSIONS.

The relation of this research, and of the other similar results which have been published, to the treat-:ment of post-operative thrombosis, is perhaps an in-:direct one. It is proved that the great majority of patients of all ages, operated upon for all sorts of conditions and by various anaesthetics, show a distinct decrease in the coagulation-time of their blood after operation, and in one case where this decrease had been very marked, fatal pulmonary embolism occurred on the 9th day. There is no evidence that rise of temp-:erature caused by sepsis or an intercurrent infection has been associated with shortening of coagulation-time. If it could be made out that climatic or atmospheric conditions were effecting a general shortening of coag-:ulation-time of normal people at certain times, or that a seasonal incidence of thrombosis was to be ex-:pected, it might be possible to advise the avoidance of all except emergency operations during these danger periods. It is suggested that this easy method of estimating coagulability might be useful in following the progress of cases of thrombosis and perhaps regul-:ating treatment.

My thanks are due to Professor Lorrain Smith for suggesting the subject of the first part to me and to Professor Wilkie for the second part, and to both for their advice and help and for giving me every facility for carrying out the research. Also to Dr. Howel-Evans, Secretary of the Status Lymphaticus Sub-committ-:ee, and the Staff and Assistants of the Pathology Department, University, Edinburgh and the Nursing Staff of Professor Wilkie's Wards for their interest.

REFERENCES

to

LITERATURE IN PART II.

1. Rendel Short & Fraser .. B.M.J. June 4, 1927, 1,001.

2. Heard .. New Orleans Med. & Surg. Journ. 1924, 451.

3. Lindsay .. Joint Discuss. No. 3 Lancet, 1925, i, 327.

4. Rupp .. Archiv. für klinishe Chirurgie, 1921.

5. Cruveilhier .. Anat. Path. Paris, 1829 - 42, quot. by 41.

6. Virchow .. Gesammelte Abhandlungen Frankf. 1856, quot. by 41.

7. Bloch .. La Coagulabilite Sang-:uine, Mesure Clini-:que These de Paris, 1914, quot. by 83.

8. Howell .. Arch. Int. Med. 1914, xiii, 76.

9. Rich .. Amer. Journ. of Physiol. 1917, 43.

10. Addis .. Quart. Journ. Exper. Physiol.I.1908, 305.

11. Gibbs .. Quart. Journ. of Med. April, 1924, 67.

12. Dale and Laidlaw .. Journ. Path, 1912, xvi, 359 and 362.

13. Read .. Journ. Amer. Med. Assoc. lxxviii, 1922, 1887.

14. Cannon .. "Bodily changes in Pain, Hunger, Fear and Rage"

15. Silbermann and Kagan .. Zentralbl. f. Chir. Oct. 9, 1926, 2,589.

16./

16. Von Eiselsberg .. Quot. by 17.

17. Lockhart-Mummery .. Sect. of Surg. B.M.J. 1924, ii, 850.

18. De Quervain .. Surg. Gynec. & Obst. 34, 3rd Jan. 1922.

19. Glynn and Knowles .. B.M.J. 1910, 1,412.

20. Mennell and Dudgeon .. Soc. of Anæsth. 1906, and 3.

21. Adler and Keller .. Quot. by 22, no ref.

22. Chauvin and Esmenard .. C.R. Soc. de biol. 1923, lxxxix, 323.

23. Straus and Rubin .. Journ. Amer. Med. Assoc. Jan. 1927, 310.

24. Hunter .. Quot. by 17.

25. Bristowe .. Trans. Path. Soc. Lond. 1870, xxi, 143, quot. by 41.

26. Pitt .. Ibid 1893, xliv, 52.

27. Box .. Trans. Clin. Soc.Lond. 1906, xxxix, 189.

28. Glynn, etc. .. Lect. & Discuss. B.M.J. Feb. 23, 1924 and Apl. 19.

29. Karsner .. Journ. Med. Research, 1912, 22.

30. Gordon-Watson .. See 3.

31. Cowell .. Lancet, July, 1919, 137.

32. Wheeler .. Med. Annual Review, 1926, 373.

33. Dale and Laidlaw .. Journ. Physiol. lii.

34. Buxton .. "Anæsthetics" 1920.

35. Elliott .. Journ. Physiol. xliv, 1912, 376.

36. Keith and Robertson .. Report VI, Med. Res. Council, quot. by 31.

37/

37.	Sherrington and Monkton	..	Proc. Roy. Soc. 1893.
38.	Cannon and Fraser	..	B.M.J. 1917.
39.	Sutton	..	B.M.J. 1918, ii, 364.
40.	Wright	..	Journ. of Physiol. 1891, xii.
41.	Welch	..	In Allbutt & Rolles-:ton's System of Med. VI. 691, etc.
42.	Cullen, Austin, etc.	..	Journ. Biol. Chem. 1923, 56, 625.
43.	Potter	..	Quart. Journ. of Med. April, 1925, 261.
44.	Pemberton & Cunningham	..	Lancet, Sept. 27, 1924.
45.	Ross and McGuigan	..	Journ. Biol. Chem. 22, 1915, 407.
46.	De Quervain	..	Schweiz. Med. Woch. 28th May, 1925.
47.	Wallis	..	Lancet, Sept. 11,1920.
48.	Simpson and Rasmussen	..	Quart. Journ. Exper. Physiol. X, 1916.
49.	Hutchison	..	See 3.
50.	Allen. etc.	..	Amer. Journ. Obstet. and Gynec. Feb.1927, 156.
51.	Addis	..	Quart. Journ. Med. 1909, ii, 149.
52.	Barlow and Ellis	..	Amer. Journ. of Physiol. 1924, 70.
53.	Briggs	..	Quot. by 41.
54.	Mulzer	..	München Med. Wchschr. 54, 1907, 408, quot. by 23.
55.	Sherrington and Copeman	..	Journ. Physiol, 14, 1893, 52.
56.	Buckmaster	..	Journ. Physiol, xli, 246.

57/

57. Bedford .. Amer. Journ. of Physiol. xliii, 1917.

58. Mendenhall .. Amer. Journ. of Physiol. xxxviii, 1915, 33.

59. Gray .. Ibid 68, 1924, 149.

60. Falls .. Journ. Amer. Med. Assoc. lxxix, 1922, 1816.

61. Parry .. B.M.J. 1925, ii, 649.

62. Cresswell .. B.M.J. 1926, i, 284.

63. Von den Velden .. München Med. Wchnschr. lviii, 1911, quot. by 14.

64. Schäfer .. "Endocrine Organs" and Proc. 17th. Int. Med. Congr. 1913.

65. Piney .. "Recent Advances in Haematology".

66. Vosburgh and Richards .. Amer. Journ. of Physiol. ix, 1903, 39.

67. Wiggers .. Arch. Int. Med. 1909, iii, 152, quot. by 14.

68. Cramer .. Journ. Physiol. 1918, lii.

69. Hannan .. B.M.J. July 2, 1927, 14.

70. Pasteur .. Bradshaw Lecture Lancet Nov. 7, 1908.

71. Wrigley .. See 28.

72. Cramer, Drew, Mottram and others .. B.J. Exper, Path. iv, 1923.

73. Owen .. B.M.J. May 28, 1927, 987.

74. Gulland and Goodall .. "The Blood".

75. Loeb .. N.Y. Med. News, lxxxvi, 1905, 577.

76. Beneke .. Quot. in Schweig. Med. Woch. 28th May, 1925.

77./

77. De Snoo .. Journ. Amer. Med. Assoc. Nov. 14, 1925.

78. A.O.W. .. B.M.J. Dec. 5, 1925.

79. Faure .. B.M.J. April, 16, 1927.

80. Fayrer .. B.M.J. 1893, i.

81. Sydenstricher, Delatour and Whipple .. Journ. Exper. Med. xix, 1914.

82. Gounet, etc. .. Lyon Medical, Dec. 5, 1926, 657.

83. Pruvost .. "Diagnostics de laboratorie" xxvii, 1924, 160.

84. Cohen, M.S. .. Arch. Int. Med. Nov.15, 1911, viii, 684.

85. Pfeiffer and Hoff .. Zentralbl. f. gynakol. 1922, quot. by 65.

86. Binger, Brow and Branch . Journ. Clin. Invest. Dec. 20, 1924.

87. Dunn .. Quart. Journ. of Med. 1920.

88. Wharton and Pierson .. Journ. Amer. Med. Assoc. lxxix, Dec. 2, 1922.