steroid hormones are likely to reawaken interest in the problems of haemopoiesis and the possible part played in them by the lymphocyte.

Summary

A quantitative technique has been employed to study the nucleated cells of the bone marrow, both in normal guinea-pigs and in guinea-pigs which were killed six hours after the administration of a single dose of A.C.T.H. or of cortical extract (eschatin).

In the normal guinea-pig red marrow was found to contain on the average 1,236,000 nucleated cells per c.mm., of which 144,800 were lymphocytes. The high lymphocyte content of bone marrow is not attributable to blood contamination.

There was no demonstrable increase of damaged cells in the marrow six hours after giving either A.C.T.H. or eschatin, but there was a statistically significant increase in the lymphocyte content after eschatin and an increase almost reaching the significant level in the case of A.C.T.H.

It is possible that increased uptake by the bone marrow of lymphocytes from the blood may be a contributory factor in the lymphopenia which may follow the administration of A.C.T.H. steroid hormones.

Whatever may be the effect of steroid hormones on lymphoid tissue in other parts of the body it has not been found possible by quantitative methods to demonstrate a destructive action on the lymphocytes of the bone marrow.

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SYMPATHECTOMY FOR HYPERTENSION

BY

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This paper presents a series of cases of severe essential and malignant hypertension which have been treated by thoraco-lumbar sympathectomy at Hammersmith Hospital since 1945, and which have been followed up in detail. A study of this material has given us some useful data on the early effects of sympathectomy for hypertension.

From November, 1945, to January, 1950, 35 carefully selected patients were operated upon. They were all in the care of the surgical unit under Mr. R. H. Franklin. Most of the operations were performed by him, the remainder by his assistants.

These patients were referred to us for surgery by the Department of Medicine or sent from other hospitals, and before submitting them to operation extensive investigations were carried out to confirm their suitability for sympathectomy.

Routine for Investigation and Criteria of Operability

Apart from a thorough clinical examination, the routine investigation of all patients included electrocardiograms, x-ray screening of the heart and lungs, a study of the fundi, and the sodium amytal sedation test. An assessment of renal function was made by urine analysis, culture, and microscopy, specific gravity studies with concentration and dilution tests, blood-urea levels, urea-clearance tests, and intravenous pyelography.

With the aid of the information provided by the foregoing investigations, patients were selected for operation on the basis of the following criteria:

1. The patient must be under 55 and preferably under 50 years of age.
2. The diastolic blood pressure must be over 100 mm. Hg and the systolic level preferably over 200 mm. Hg.
3. There should be definite symptoms referable to hypertension, particularly severe headaches or disturbances of vision.
4. The patient must not be in cardiac failure.
5. Renal function must be adequate—that is, a blood-urea level of under 50 mg. per 100 ml. and a urea-clearance value of over 50% of normal. The intravenous pyelogram should not show any gross defect in outline or in rate of excretion.

6. If there has been a previous cerebral vascular accident the patient must have recovered from it without any serious residual disability.

7. The circulation should be labile—that is, capable of responding to rest in bed or to a sedation test by a fall in the diastolic B.P. level of at least 20 mm. Hg.

8. Malignant hypertension as demonstrated by the presence of papilloedema is a definite indication for surgery provided that the patient is not in the terminal stages of the disease with cardiac or renal failure.

Surgical Technique

In our first 14 patients the operation performed was the well-known extrapleural thoraco-lumbar sympathectomy of Smithwick (1940).

In May, 1948, we altered our technique to one of transpleural thoracotomy and sympathectomy, as it was noticed that during thoracotomies for other conditions an excellent view of a considerable extent of the thoracic sympathetic chain and its branches could be obtained, and, in addition, open thoracotomy permitted a thorough re-expansion of the lung under direct vision at the end of operation.

This approach has remained in use up to the present and has been carried out 41 times on 21 of our patients.

Details of the Operation

General anaesthesia with thiopentone, cyclopropane, oxygen, and curare, respiration being controlled through a cuffed endotracheal tube, is used. The patient is placed in the lateral position with the side to be operated on uppermost. A wedge is placed under the lower ribs, and the arms are drawn forwards away from the chest on supports. An incision approximately 10 in. (25 cm.) long is made in the line of the eighth rib and is carried down to the rib. Bleeding points are coagulated with diathermy. A segment of the eighth rib between the angle and the costochondral junction is resected subperiosteally. At this stage the intercostal nerve at the lower edge of the rib bed is found and a few inches of it close to the angle of the rib is excised. We believe that this procedure reduces the incidence of post-operative pain.

The pleura is next opened along the bed of the rib and the lung is permitted to collapse. Rib spreaders are inserted and the lung and diaphragm retracted by an assistant. The great splanchnic nerve is the most easily visible branch of the thoracic sympathetic trunk, and can be clearly seen through the pleura overlying the sides of the vertebral bodies near the diaphragm. The pleura is incised at this place and the great splanchnic nerve is picked up and followed cranially to its highest origin from the sympathetic trunk at the level of the sixth (or sometimes the fifth) thoracic ganglion. The ganglionated chain is then traced downwards to the diaphragm by incising the pleura over it. The diaphragm is now elevated by blunt finger or gauze dissection from the posterior abdominal wall at the point where the chain passes under it and an illuminated retractor is inserted into the space so made (deep to the medial lumbo-costal arch) and the upper lumbar chain is exposed. In this way the first lumbar ganglion (where this is present) is brought into view, and with suitable retraction it is sometimes possible to see the second lumbar ganglion. Only very rarely is it possible to see the lumbar chain caudal to this by simple retraction.

The chain over an extent from the sixth thoracic ganglion to the first lumbar ganglion inclusive, together

FIG. 1.—Typical specimens of the sympathetic ganglionated chain with the splanchnic nerves as removed in the transpleural operation.

with the splanchnic nerves, is thus exposed and is resected (see Fig. 1). This resection is performed between Cushing's silver clips in order to control any small vessels which run with the nerves and so that the clips could act as markers in post-operative x-ray films to confirm the extent of removal of the sympathetic chain. Where there is a strong clinical suspicion of the presence of an adrenal tumour (phaeochromocytoma) and it is considered necessary to explore that organ, the diaphragmatic origin is divided with scissors and a satisfactory approach obtained.

The lung is next reinflated by the anaesthetist and any segment which remains collapsed in spite of positive endotracheal pressure may be expanded by massaging air into it from a neighbouring segment until the lung is completely aerated.

The chest is now closed in layers with catgut without drainage, but in those cases in which there is a tendency to ooze within the pleura an intercostal catheter is inserted into the chest through a separate stab incision and drained into an underwater seal for 48 hours.

The opposite side is similarly treated two to three weeks later.

Material

Between November, 1945, and January, 1950, 35 patients were operated on (23 women, 12 men). The youngest patient was aged 20 and the oldest 53. The average age at operation was 41.5 years. Of the 35 patients, 24 had essential hypertension and 11 had malignant hypertension as shown by the presence of papilloedema.

Sixty-eight operations were performed; in two patients only one side of the operation was completed. Twenty-seven operations were of the extrapleural Smithwick type and 41 were of the transpleural variety. We have maintained contact with 33 of these patients, mostly by their regular attendance at the follow-up clinic. A few patients living too far from London for routine attendance have been followed by corresponding with them and with their family doctors. Two patients are untraced. These 33 patients have been followed up for

a period varying from 2 to 51 months from operation—the average period of follow-up has been 18.5 months in those with essential hypertension and 18 months in those with malignant hypertension.

The results of sympathectomy for hypertension in these patients are considered under the following headings: (a) the effects on the blood-pressure levels; (b) the relief of symptoms; (c) the production of adverse symptoms; and (d) morbidity and mortality of the operation.

Effects on the Blood-pressure Levels

Certain standards of recording B.P. levels have been adopted, and these together with some definitions are quoted to make the use of subsequent terms clear.

All B.P. levels have been taken with the patient recumbent after a period of rest of at least five minutes. The B.P. level "before operation" represents the figure recorded on the day of admission to hospital. The B.P. "after operation" is the level recorded just before the patient's discharge from hospital, and the B.P. "at present" is the level measured at the out-patient clinic on the visit closest to January 1, 1950.

In order to reduce the mass of recordings to a more easily appreciated form, an arbitrary scale of classification has been chosen. It is generally agreed that in hypertension the diastolic B.P. level is a more reliable measure of the severity of the disease than the systolic B.P. Furthermore, since diastolic levels are less liable to the gross fluctuations which are observed in the systolic levels in response to emotion or exertion, our results have been classified on the basis of change in the diastolic levels. A fall in the diastolic level of 20 mm. Hg or more is considered to represent a "significant" improvement, a fall of 19 mm. Hg or less represents "no change," and where the diastolic level has in fact risen after operation the change is recorded as "worse."

In the 24 cases of essential hypertension that have been treated the effect of sympathectomy on the diastolic levels "after operation" was to produce a "significant" fall in 17 cases and "no change" in six cases. One patient died during the second stage of the operation (see Table I). The levels recorded "at present" after

TABLE I.—Blood Pressure Changes After Sympathectomy

No. of Cases Completing Operation	B.P. Changes "After Operation"	B.P. Changes "At Present"
Essential hypertension (24)	Significant fall .. 17 No change .. 6 Died during operation 1	Significant fall .. 6 No change .. 13 Worse .. 1 Died .. 3 Untraced .. 1
Malignant hypertension (9)	Significant fall .. 7 No change .. 2	Significant fall .. 2 No change .. 4 Died .. 2 Untraced .. 1

an average follow-up period of 18.5 months show that only six patients have maintained a "significant" improvement in B.P., 13 show "no change," one is worse, three are dead of the disease, and one is untraced.

Thus we see that only 6 out of 24 of our patients (25%) have so far maintained a "significant" fall in the B.P. level since operation.

Eleven patients with malignant hypertension were operated on, but in two of them only one side of the operation was completed: one because of fulminating progress of the disease after the first stage, terminating in death three months later; the other, who was dis-

charged from hospital between stages, failed to return for the second operation, and died 34 months later of the effects of the disease. Of the nine patients in whom both sides of the operation were completed, seven had a "significant" fall in B.P. "after operation" and two had "no change." "At present," after an average follow-up period of 18 months, only two patients have maintained a "significant" fall in B.P.; four show "no change," two died from the disease, and one is untraced (see Table I).

Thus we see that six out of nine patients are alive after an average of 18 months and only two of these have maintained a significant improvement in blood pressure.

Relief of Symptoms

With respect to the relief of symptoms our patients have fared considerably better. Before sympathectomy all had symptoms due to hypertension. The commonest was headache, often of a severe and incapacitating nature. Another frequent complaint was disturbance of vision sometimes approaching complete blindness. Other symptoms included breathlessness, tiredness, inability to concentrate, epistaxis, angina of effort, and those symptoms associated with cerebral vascular accidents.

Amongst 24 patients with essential hypertension, 23 have been followed up to "the present." Of these, 16 are virtually symptom-free and at full work, two have had partial relief, two are unaffected symptomatically, and three are dead (Table II).

TABLE II.—Symptomatic Relief Following Sympathectomy

No. of Cases Completing Operation	Symptomatic Changes "At Present"
Essential hypertension (24)	Symptom-free .. 16 Partial relief .. 2 No change .. 3 Died .. 3 Untraced .. 1
Malignant hypertension (9)	Symptom-free .. 4 Partial relief .. 2 Died .. 2 Untraced .. 1

Of nine patients with malignant hypertension who underwent both sides of the operation, four are virtually symptom-free "at present" and at work, two have obtained only partial symptomatic relief and are semi-invalids, two are dead of the disease, and one is untraced (Table II).

Production of Adverse Symptoms

Side-effects associated with bilateral thoraco-lumbar sympathectomy in our patients have been common enough to merit detailed consideration.

1. *Pain and Hyperaesthesia.*—A neuralgic pain or a zone of hyperaesthesia radiating along the side of the chest to the epigastrium referred to thoracic segment 8 (or 9) has developed in 11 of the 35 patients. This effect has appeared within the first few weeks after operation, and has in all cases disappeared after a few months. The pain has been of varying intensity, sometimes minor but sometimes of enough severity to require attempts at intercostal nerve block for its relief. We believe that since the practice of deliberately excising a portion of intercostal nerve at operation was introduced the incidence and severity of this effect have been reduced. Generally the pain or hyperaesthesia is well tolerated, and the patients will endure it without distress provided they are reassured of its benign nature and early disappearance.

2. *Post-operative Compensatory Sympathetic Effects.*—It is now well recognized that after major excisions of the

sympathetic nervous system the residual portion becomes hypersensitive to the stimuli which normally activate it. In this respect, six of our patients have developed vasospastic manifestations of a subjectively noticeable degree. This effect has appeared in varying grades of severity, the least severe being an increased sensitivity to cold. Intermediate grades have appeared with the sensation of "pins and needles" in the toes and fingers, and the most severe with attacks of pallor in the fingers resembling a form of Raynaud's phenomenon but arising spontaneously and not necessarily in response to cold or to emotion.

All these effects have been temporary and not incapacitating. One of our patients, an Anglo-Indian lady, developed a temporary hyperhidrosis of the palms and fingers which subsided in the course of a few weeks.

Only four of our patients developed post-operative postural hypotension, with a feeling of faintness on rising after a period of recumbency. Again this has not persisted for more than a few months.

Morbidity and Mortality of the Operation

In operating close to or within the pleural cavity we have found it common for our patients to develop minor post-operative chest complications, usually of the nature of small effusions of clear or blood-stained fluid or very small collections of air. These minor complications have for the most part resolved spontaneously or following one or more aspirations of the chest.

Chest complications of a more serious nature that have occurred in five patients are listed separately in Table III. Major complications outside the chest

TABLE III.—Post-operative Chest Complications

Nature of Complication	No. of Cases	Type of Sympathectomy	Treatment of Complication and Result
Haemothorax	1	Transpleural	Open evacuation of clot and resuture of chest. Cured
Atelectasis of lung	1	"	Bronchoscopic aspiration of mucus and breathing exercises. Cured
Valvular tension pneumothorax	1	Smithwick	Continuous pleural aspiration. Cured
Chylous pleural effusion	1	Transpleural	Repeated aspiration of chest. Cured
Empyema thoracis	1	"	Decortication after sterilization of pus with streptomycin. Cured

occurred in three patients: one developed a haemoperitoneum from spontaneous rupture of the vessels at the splenic hilum during convalescence, which was cured by ligation and splenectomy; one developed a deep phlebothrombosis of the calf veins, which resolved under heparin; and one female patient, 18 weeks pregnant, miscarried after a Smithwick operation for malignant hypertension.

In 68 operations we have only had one fatality—an operative mortality of approximately 1.5%. This compares favourably with Smithwick's (1948) series, which had an operative mortality of 2.2%.

We have not had a death so far from the transpleural sympathectomy. Our single operative death occurred during the second stage of a Smithwick sympathectomy in February, 1947. The patient was a diabetic woman aged 49 with severe essential hypertension who suffered a considerable fall in blood pressure immediately after the division of the sympathetic chain; in spite of all attempts at resuscitation she died on the table of acute peripheral circulatory failure. Nowadays, the patient would probably have survived this crisis with the use of methylamphetamine hydrochloride *B.P.C.*, a drug

which we have since found to be a vasopressor agent of great value in controlling hypotension during and after operation.

Post-operative Tests of Sympathetic Denervation

In 12 patients I carried out a series of dye sweating tests at various stages in an attempt to correlate the extent of denervation with the area of loss of reflex sweating.

In those patients in whom the denervation extended from the ganglia T6 to L1 inclusive, photographic sudograms were obtained showing zones of absent sweating over the spinal dermatomes T6 to T11 plus variable patchy extensions into dermatomes T12 and L1 (see Fig. 2).

FIG. 2.

FIG. 3.

FIG. 2.—Photograph showing the zones of absent reflex sweating (unstained) after resection of the sympathetic chain from ganglia T4 to L1 inclusive on the right side and T6 to L1 inclusive on the left side. The lower boundaries are patchy, and sweating still persists in the "bathing-trunk" area, indicating residual sudomotor activity in this zone.

FIG. 3.—Sudogram in a patient following resection of the sympathetic chain down to and including ganglion L2 on the right side and L1 on the left side. The right lower limb is "dry" except for a wide zone of residual sweating on the front of the thigh. The left lower limb sweats except for a patch on the upper thigh.

When the level of section of the chain was below the ganglion of L2 sweating in the shin and foot was almost completely lost; it was retained to a variable degree in the thigh, and completely retained in the groin folds and in the pubic and medial crural areas (dermatomes T12; L1, and L2) (see Figs. 3 and 4).

This finding is in agreement with those of Ray and Console (1948), and confirms the presence of residual sudomotor pathways to dermatomes T12, L1, and L2 after resection of the ganglia T12, L1, and L2. This is probably explained, as suggested by Boyd and Monro (1949), by the presence of "intermediate" ganglia carrying sudomotor fibres situated outside the main sympathetic trunk which therefore remained behind after sympathectomy.

Discussion

We now operate as a routine by the transpleural route because of the simplicity and ease of approach to the lower thoracic chain and its branches. This

FIG. 4.—Sudogram of another patient following a resection; the lower limits are identical with those in the patient shown in Fig. 3. The overall picture of absent sweating is similar to that in Fig. 3, but the zone of residual sweating in dermatomes T 12, L 1, and L 2 is considerably less.

route has the disadvantage of not often permitting a view of the lumbar chain below the first lumbar ganglion; but this we believe is only a minor disadvantage, as there is no conclusive evidence that the additional removal of ganglia L 2 and L 3 significantly improves the results. We are therefore content to section the lumbar chain as low as our approach permits—that is, usually just below the ganglion of L 1.

Smithwick (1950) states: "It is my belief that a thorough denervation of the splanchnic bed, such as is obtained by removing the sympathetic trunks bilaterally from the eighth thoracic to the first lumbar ganglion inclusive, together with the splanchnic nerves, is the procedure of choice for most cases." This can be very readily achieved by the transpleural route.

In order to obtain a statistically significant evaluation of the results of sympathectomy for hypertension it is necessary to follow a large classified series of cases treated by

surgery for at least 10 years and to compare it with a similar series treated medically. Nevertheless the results of the follow-up of this small series is of value, for even at this early stage an appreciation of the value of the operation has been obtained and the trend of the results is becoming apparent.

With regard to severe essential hypertension the early post-operative fall in B.P. was satisfactory in 17 out of 24 cases, but only 6 cases maintained this improvement after an average of 18 months. If we consider these results of the B.P. changes alone, a pessimistic view of the operation could be taken, but it is also necessary to allow for the symptomatic relief which the operation has achieved for our patients.

At present 16 of the original 24 patients (66.6%) are virtually symptom-free and have returned to normal work. This in my opinion represents a result of considerable value. Furthermore, the gratitude which has so often been expressed by individual patients for the relief of distressing symptoms has convinced us that the operation is worth while in spite of the failure in many cases to achieve any satisfactory fall in B.P. There is also evidence (Smithwick, 1948) that sympathectomy persistently reduces or even abolishes those rises of blood pressure which are normally caused by reflex vasoconstriction, and it is likely that this mechanism protects the circulation against dangerous physiological elevations of pressure and can be regarded as a favourable effect of operation even in those cases in which the B.P. levels have not fallen significantly after sympathectomy.

In the nine patients with malignant hypertension who have completed both sides of the operation and have

been followed for an average period of 18 months, six are known to be alive, and four of these are virtually symptom-free and at work.

As approximately 80% of patients with malignant hypertension die in the first 12 months of the disease in spite of medical treatment (Keith, Wagener, and Barker, 1939), these results indicate a definite benefit following surgery.

On theoretical grounds it would seem logical to operate on the mildest cases of essential hypertension in the hope of halting the progress of the disease, but we have refrained from doing this, since these are just the cases in which there is relatively a better prognosis without surgery and in which it is difficult to judge the outlook in the individual case. Furthermore, in the absence of symptoms, it is probably unjustifiable to operate for mild hypertension and submit the patient to the hazards of morbidity and mortality.

Conclusions

So far, a closer study of the more successful of the results of our treatment of essential hypertension reveals that they occurred most often in women who had developed a severe hypertension after a pregnancy complicated by toxæmia or eclampsia.

In malignant hypertension our best results to date have been obtained in patients operated on in the early stages of the disease, before the heart and kidneys were seriously impaired.

A survey of those cases which derived least benefit from sympathectomy reveals that they were mostly in the older age groups, particularly over 49, or had suffered from borderline or established cardiac failure before operation. One patient with essential hypertension due to an undetected chronic pyelonephritis was submitted to sympathectomy, but after a period of six months' relief the hypertension entered the malignant phase and she died in uræmia 40 months after operation. Chronic pyelonephritis should be carefully sought for before operation, since it may be possible to remove a kidney for unilateral disease, to the benefit of the patient.

The list of criteria of operability given earlier in this paper summarizes our present views on this matter, although fulfilment of these criteria does not guarantee that the patient will benefit from sympathectomy.

It should be remembered that sympathectomy for patients with severe hypertension is a palliative measure and that in the long run these patients will die of the effects of hypertension. Sympathectomy can, however, be applied with benefit to a group of carefully selected patients, and as it makes life more tolerable for most of them, and seems to prolong the useful duration of life in some, particularly the malignant cases, it appears at this interim stage to be a procedure of value.

Summary

This paper presents an interim survey of 35 cases of severe essential and malignant hypertension which have been treated by thoraco-lumbar sympathectomy at Hammer-smith Hospital since 1945.

The criteria of selection for operation are summarized, and the technique of the transpleural sympathectomy is described in detail.

After a follow-up period varying from 2 to 51 months (average 18 months) the survey reveals that so far only 25% of the patients have maintained a significant fall in

blood pressure, but that 66% of them have been relieved of incapacitating symptoms and have returned to work.

The prognosis for malignant hypertension so far shows a definite improvement as a result of sympathectomy.

For a limited but definite group of patients with hypertension, sympathectomy is a valuable procedure.

I wish to thank Mr. R. H. Franklin for permission to publish his cases and for his valuable advice in the preparation of this paper.

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THE EFFECT OF A.C.T.H., CORTISONE, AND D.C.A. WITH ASCORBIC ACID ON "FORMALIN-ARTHRITIS"

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In 1949 Selye produced an arthritis in rats by injecting formaldehyde solutions into the feet. He said that adrenocorticotrophic hormone (A.C.T.H.) and "cortisone" prevented the acute and chronic stages of "formalin-arthritis," having an action opposite to that of deoxycortone acetate (D.C.A.), which exacerbated the condition. He further asserted that the lesions of "formalin-arthritis" resembled, microscopically, in the acute oedematous stage the rheumatic, and in the chronic stage the rheumatoid, type of arthritis.

In clinical treatment Lewin and Wassén (1949) and later among other workers, Le Vay and Loxton (1949) reported that the treatment with D.C.A. and ascorbic acid parenterally was effective in cases of rheumatoid arthritis. This has been disputed by many workers (Empire Rheumatism Council, 1950).

Below we report our experience with "formalin-arthritis"; the histological picture of this condition will be presented elsewhere (Bourne, 1951; Bourne, Parkes, and Wrigley, 1951).

At an early stage in the work it was recognized that means should be sought for estimating quantitatively the changes in limb volume which occurred. Selye gave no indication that more than visual observation was employed; and indeed his illustrations would support the impression that the differences to be observed were sufficient for subjective evaluation to be adequate. Brownlee (1950), however, followed the changes in limb volume in the course of development of "formalin-arthritis" in rats by calliper measurements. The method we used (Bergel, Parkes, and Wrigley, 1951) consists in photographing a limb in such a way as to

obtain a negative silhouette, which is cut out and weighed. Twelve such shapes provide enough paper for reasonable accuracy in weighing. Duplicate exposures are made of front and side aspects of the limb in groups of six rats, and the silhouettes are bisected into regions corresponding respectively to "foot" and "ankle," which are the parts affected by the acute and chronic stages of "formalin-arthritis." The product of the weights of corresponding front and side shapes serves as an index of limb volume for the group.

It was considered of importance that work should be accompanied by some knowledge of the histological changes attending the course of "formalin-arthritis." Consequently, a series of rats were injected with formalin (see below) and killed after the elapse of a period varying from five minutes to four weeks. Limb volumes were measured before injection and immediately before sacrifice. Ankle-joints and adrenals were sectioned, the histological details of which are reported in another paper (Bourne, 1951). They show that with increase in the period following injection there is a progressive increase in the degree of inflammatory reaction of the ankle-joint of the injected limb, which is followed to a smaller degree by changes in the joint of the contralateral limb. At the same time there is a progressive decrease in lipid content of the adrenal cortex. These changes can be correlated with the alteration in swelling of the injected foot and ankle. However, while there appears to be a return of the histological appearance of the contralateral ankle-joint to normal, the degree of inflammation of the joint of the injected limb increases still further. By the end of the fourth week after injection all limb volumes have returned to normal.

FIG. 1.—Showing the degree of correspondence between the course of the lesion histologically and the changes in limb volume.