

culosis were more severe and virulent as evidenced by the four deaths. Their parenchymal lesions appeared sooner after the initial effusion and tended to be more extensive, four being bilateral, two of these presented cavity formation, and two developed renal tuberculosis.

In the negative culture group the parenchymal lesions appeared after a longer interval and were less extensive, most of the cases presenting as minimal lesions, two were bilateral

TABLE VI.  
TIME INTERVAL UNTIL OTHER MANIFESTATION OF  
TUBERCULOSIS

	Positive culture group	Negative culture group
2 months.....	3 cases	1
4 " .....	4	1
6 " .....	3	0
8 " .....	2	0
10 " .....	1	3
1 year.....	1	3
1½ years.....	0	2
2 " .....	2	3
3 " .....	1	1
4 " .....	1	0
5 " .....	0	1
6 " .....	0	1

and no cavity occurred in this group. Two cases developed ischio-rectal abscesses and one renal tuberculosis.

The cases that have remained well to date practically all have fairly extensive pleural adhesions but these are slowly but progressively resolving over each succeeding year. There is a definite group of individuals complaining of vague ill health in which one finds it difficult to distinguish true symptoms from a desire to retain or increase their pensions.

#### SUMMARY

In this series of seventy-eight cases of idiopathic pleurisy with effusion there was no previous history suggesting tuberculosis. Enlistment chest x-rays taken shortly before the onset of pleurisy were negative. The more pleural fluid cultures that are taken, the higher will be the portion of cases proved to be tuberculous in etiology.

The character of the symptoms, clinical findings and course of the cases was essentially the same whether the pleural fluid cultures were positive or negative for tubercle bacilli. There were differences in degree inasmuch as fluid

appeared sooner after the onset of symptoms in the positive group and persisted longer.

In incidence of subsequent tuberculosis, the number was the same in both positive and negative groups; however, the disease manifests itself after a shorter interval in the positive culture group, and was of a more serious and extensive nature.

The above differences probably are dependent on the virulence of the infecting organism, massiveness of infecting dose, and the degree of the individual's resistance.

There can be little doubt that primary or idiopathic pleurisy with effusion is an early or primary manifestation of tuberculous infection, and the incidence of other later manifestations of tuberculosis is high.

Patients with this diagnosis, whether pleural fluid cultures are positive or negative, should be treated as tuberculosis with a prolonged period of supervised bed rest, probably three or four months, after clinical signs of active infection have subsided.

I should like to express my appreciation for the cooperation and help given me in this survey by Dr. W. P. Warner and Dr. G. A. Winfield; also to compliment the Department of Veterans' Affairs on the thorough manner in which they are following up these cases.

#### NEEDLE BIOPSY OF THE LIVER

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THE complexity of hepatic physiology tends to render the use of any one of the liver function tests of limited value and when a battery of tests is employed, the results do not necessarily clarify a difficult diagnosis. Some clinical method of study of actual morbid histology in disease processes as they affect the liver is, therefore, of paramount importance. For this purpose, there are several procedures available.

1. *Surgical biopsy.*—Of necessity, this involves procedures both expensive and of a major character which are seldom warranted. Many cases are unsuitable owing to severity or danger of exacerbation of the condition and to limited accessible liver surface. In addition, the effect of anaesthesia and surgical trauma on the liver may distort the resultant patho-

logical findings. This was strikingly seen in one of our cases.

2. *Peritoneoscopy*.—Though less traumatizing, the question of expense and availability for routine work again arises. This procedure is painful and unsuitable for serial studies. As with laparotomy, accessible liver tissue is small and, of necessity, superficial. Though Hoffbauer<sup>1</sup> has combined 'needle biopsy and peritoneoscopy with success, we have not felt ourselves justified in such a complicated procedure.

3. *Needle biopsy*.—For some time we have been using this method in cases where it appeared to be indicated. It is a relatively minor procedure, consisting in the punching out of a small cylinder of liver tissue with a 1 mm. bore needle thrust through the parietes. This procedure is one which may be performed at the bedside with a minimum of inconvenience to the patient. Although it is most applicable to diffuse hepatic lesions, it is surprising how frequently localized carcinomatous metastases may be revealed. Volwiler and Jones<sup>2</sup> in fact, report two cases of metastatic carcinoma missed on peritoneoscopy, which were later diagnosed by needle biopsy. The procedure is not devoid of certain dangers, chief of which are hæmorrhage from tear of the liver, damage to neighbouring structures, and infection.

A small amount of bleeding of the order of 5 to 10 c.c. is almost invariable, but gross hæmorrhage is rare when suitable selection of cases and control of the postoperative period is observed.<sup>2</sup> Deaths are reported due to uncontrolled intraperitoneal hæmorrhage in the hands of skilled operators<sup>1, 2, 4, 7</sup> and the procedure is not one to be performed lightly nor anywhere remote from available blood transfusion and surgical services. Tear of the liver may occur if the patient should breathe during biopsy. This hazard is minimized by careful explanation, good local anæsthesia, and rapid performance of biopsy. Perforations of the transverse colon, gall bladder, or large cœliac vessels have been reported in a few cases.<sup>1, 2</sup> With reasonable care, exogenous infection can be avoided. The possibility of a flare-up in a suspected suppurative cholangitis or multiple abscesses, precludes biopsy in such conditions.<sup>1</sup> It should be appreciated that these dangers are rarely encountered. Over 2,000 cases have now been reported in the medical literature with an

overall mortality rate of approximately 0.6% and Sherlock records 750 cases without a single fatality.<sup>4</sup>

To minimize the dangers, however, four absolute contraindications must be observed: (1) Poor co-operation on the part of the patient; (2) Severe bleeding tendency; (3) Tuberculous or other abscess; (4) Abnormal bleeding, clotting and prothrombin times.

#### METHODS OF NEEDLE BIOPSY

A large number of special instruments have been devised for the purpose.<sup>2, 3, 6, 7</sup> We use a 4-inch, 15-gauge needle with a fitted trochar, which is ground to a four-sided pyramidal tip. When the trochar is removed, a four-toothed cannula remains (Fig. 1).

There are two chief methods of approach: (a) The transpleural or lateral approach through the ninth or tenth intercostal space in the right anterior or mid axillary lines. (b) The anterior, either to the right or left of the xiphoid or at varying points beneath the

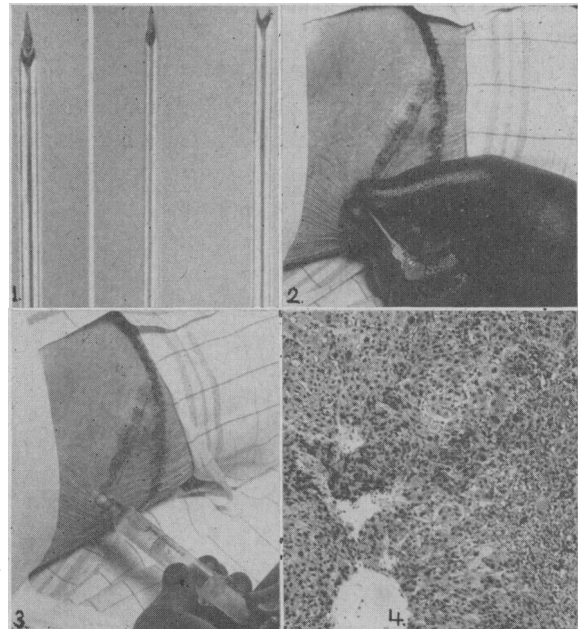


Fig. 1.—Detail of biopsy needle x2. On the left is the needle with stilette *in situ*. On the right, needle and stilette are disassembled to show toothed needle. Fig. 2.—Insertion of stilette and needle until "diaphragmatic rub" is felt. Fig. 3.—Stab biopsy movement under reduced pressure. Fig. 4.—Acute infectious hepatitis at ten days (100x).

right costal margin. We have used both methods but have favoured the lateral approach except in cases of probable malignancy where palpable nodules present and may be transfixated anteriorly. Our technique is a modification of that described by Iverson and Roholm<sup>3</sup> and also by Sherlock.<sup>4</sup> The reasons for this preference are that it may be used with safety in the absence of hepatomegaly, also the liver is biopsied in its maximum diameter and there is, therefore, less danger of penetration with damage to other viscera. Furthermore, it is possible that hæmostasis is assisted by apposition of the liver and diaphragm by this approach.

#### TECHNIQUE

1. *Selection of cases*.—The patient must be fully co-operative. It is important also to

estimate bleeding, clotting and prothrombin times prior to biopsy. Clotting time in excess of 10 minutes and prothrombin time of less than 60% of normal are contraindications.

2. *Preparation.*—All patients are given mild barbiturate premedication one hour prior to biopsy. To ensure maximum glycogen content of the parenchymal cells, biopsy is performed two hours following a high carbohydrate meal. Two bottles of cross-matched blood are available as recommended by other workers<sup>2, 4</sup> but routine use of vitamin K has not been found necessary. In moderate ascites, some assistance is afforded by a pillow beneath the left thorax.<sup>4</sup> Massive ascites should be drained prior to biopsy. It is most important to percuss out the borders of liver and to mark them on the chest wall. The chosen intercostal space is likewise marked clearly in indelible ink. The skin is treated with a mild antiseptic.

3. *Anæsthesia.*—The procedure should be completely painless. To ensure this, we have found 10 to 15 c.c. 2% procaine is usually necessary. Infiltration with local anæsthetic agent must include the liver capsule which in a high proportion of cases appears to contain pain fibres and adrenalin should not be added to the local anæsthetic if occasional severe reactions are to be avoided. It is important that one employ definite landmarks to obviate tear of the liver (Fig. 2). The pleural surface of the diaphragm is readily appreciated with the biopsy needle but not so readily with the fine needle used for local infiltration. If the patient breathes during the early part of the procedure, the base of the needle will at first move downward with each inspiration until the diaphragm has been reached, when a harsh, gritty sensation may be imparted as the needle rubs over the diaphragm. Any further advance into the diaphragm causes an immediate change in the excursion of the base of the needle which now moves upward with each inspiration. This change is a danger signal because it means that the point of the needle is either in, or through, the diaphragm; and if through, might damage the liver. The needle should be withdrawn slightly, the patient instructed immediately to exhale and cease breathing momentarily while infiltration of diaphragm and liver capsule is rapidly carried out.

4. *Biopsy.*—For actual biopsy, a skin nick is made and the biopsy needle is advanced until

the diaphragmatic rub is felt. The patient hyperventilates and ceases breathing in the fully exhaled position while the needle and trochar are inserted 1 cm. through the diaphragm into the liver substance as recommended by Sherlock,<sup>4</sup> to produce a slit, rather than round hole in the capsule. The trochar is then removed, a 5 c.c. "Luer-Lok" syringe containing 1 c.c. saline attached (Fig. 3), aspiration applied and a rapid stab in and out performed under negative pressure which is maintained until the needle has been removed from the chest wall. Saline is used in the syringe to minimize trauma to the biopsy specimen and to wash it free of blood clot.

5. *Postoperative period.*—A mild analgesic is all that is required, particularly as cases of extensive liver disease tolerate morphine poorly. We keep the patient strictly in bed for 18 hours after biopsy and estimate the pulse and blood pressure every two hours. Gilman<sup>6</sup> allows his patients up and about the ward within an hour or two but most authorities insist on 24 hours in bed.<sup>2, 4, 7</sup> Volwiler and Jones<sup>2</sup> advise immediate return to bed for a further 24 hours if any pain is felt on ambulation. Gilman<sup>6</sup> has found procaine infiltration of the needle track a sure method of alleviating postoperative pain but we have never found pain severe enough to require this.

## RESULTS

Our series includes 57 cases in which 75 biopsies were performed. Minor and transient reactions were encountered in two cases, with fall in blood pressure, accelerated pulse, dizziness, and pallor. About half of the patients complained of minor pain at the site of the puncture, in the right shoulder, or in the epigastrium, lasting not more than 18 hours.

Table I is a list of the 57 cases according to diagnosis. It is of interest that biopsy was of most diagnostic value in the cases of early portal cirrhosis, biliary cirrhosis and fatty change, and in a proportion of the cases provided an earlier and more conclusive answer than any other method. In the six cases of carcinoma there were three in whom the diagnosis had been unsuspected prior to biopsy. Of equal importance are 14 cases in which liver disease suspected clinically, was considered very unlikely in view of biopsy findings. These patients were for the most part men with a

history of hepatitis during service, upper abdominal symptoms and questionable enlargement of the liver.

From the point of view of diagnosis, the liver function tests used during the period of this study consisted of, (1) Serum bilirubin quantitative. (2) Urinary urobilinogen (dilution method). (3) Total serum proteins and A/G ratio. (4) Cephalin cholesterol flocculation test. (5) Serum alkaline phosphatase. (6) Blood cholesterol. (7) Prothrombin time and its response to vitamin K.

Since that time the bromsulphalein and thymol turbidity tests have been added, also quantitative urinary and faecal urobilinogen estimations. We have noted what is probably a common experience, that with increasing accuracy in the performance of these tests, and improved experience in their interpretation the number of patients in whom we would regard biopsy as essential to diagnosis has decreased considerably. Nevertheless, we regard it as a useful and sometimes conclusive procedure in some doubtful cases.

TABLE I.

Disease	Cases
Infectious hepatitis,	
Acute, non-fatal .....	9
Fatal .....	1
Obstructive jaundice .....	5
Cirrhosis,	
Portal, early, minimal .....	2
Advanced, active .....	3
Biliary .....	2
Carcinoma .....	6
Fatty change .....	5
Blood dyscrasias .....	4
No disease .....	14
Carcinoma, probable, (missed) .....	1
Experimental .....	5
	57

The following case histories illustrate the value of biopsy in elucidating the diagnosis in confusing cases of liver disease.

*Infectious hepatitis.*—The essential change<sup>7, 8, 9</sup> is a disorganization of hepatic architecture from the three causes; necrosis, inflammation, and simultaneous regeneration. Biliary drainage is upset as evidenced by granular pigmentation of cells and bile stasis in canaliculi but this is a secondary change. In the fatal type, a massive necrosis of all but the peripheral zones of lobules dominates the picture.

CASE 1

F.R., a 50-year old man with painless jaundice, nausea, and abdominal fullness, one week. Liver was enlarged,

firm, smooth, slightly tender, and the spleen was impalpable. Biochemical tests suggested a purely obstructive cause. Urinary bile was 4 plus, urine urobilinogen negative; van den Bergh direct positive, serum bilirubin 20.4 mgm. %; cephalin cholesterol flocculation negative; serum alkaline phosphatase 26.5 King units. Aspiration biopsy of the liver on the tenth day of jaundice left no doubt regarding the diagnosis of parenchymatous damage. The tissues showed distortion of hepatic architecture due to swelling and necrosis of central and mid-zone cells, and inflammatory cell infiltration. The hyaline degeneration described by Mallory<sup>7</sup> was evident in many of the cells (Fig. 4).

Another biopsy three weeks later showed marked regeneration occurring simultaneously with residual inflammation.

*Obstructive jaundice.*—The histological picture is primarily one of bile stasis with normal sinusoidal arrangement of liver cells and only in the later stages is necrosis found.

CASE 2

G.P., aged 71, with complaints for two weeks of eructations, anorexia, and crampy right upper quadrant boring pain, and of mild jaundice for three days.

He was an afebrile elderly man, moderately jaundiced, with slightly enlarged, smooth, tender liver. Murphy's sign was positive. Biochemistry showed urinary bile 4 plus, urinary urobilinogen negative. Stools became clay-coloured. Serum bilirubin 13 mgm. %. Total serum proteins 4.32% with a normal albumen-globulin ratio. The clinical impression was that of obstructive jaundice due to cholelithiasis. Liver biopsy showed metastatic adenocarcinoma with evidence of bile duct obstruction.

CASE 3

SECONDARY CARCINOMA

C.T., aged 76, had suffered for 18 months with exfoliative dermatitis and generalized rubbery adenopathy. Two biopsies of skin and of both inguinal and axillary glands showed chronic inflammation only. Repeated blood counts and two sternal marrow punctures had failed to demonstrate any blood dyscrasia. Hepatomegaly was noted and the liver edge was firm, tender and nodular. Laboratory tests showed serum bilirubin 1.3 mgm. %; cephalin cholesterol flocculation 2 plus and prothrombin activity 40%, rising only to 46% after the parenteral administration of vitamin K. Bleeding and clotting times were normal and despite the low prothrombin activity and frailty of the patient, aspiration biopsy of one of the palpable nodules was performed. Metastatic carcinoma was disclosed and confirmed one month later when a minute carcinoma of the caecum with massive secondary involvement of the liver was found at autopsy.

CASE 4

FATTY CHANGE

R.J.D., aged 44, an asthmatic, complained of occasional post-prandial epigastric pain, lasting about ten minutes, and of easy fatigue over the past two years. He was a sporadic heavy drinker. The liver extended 4 cm. below the right costal margin and the edge was firm, smooth and non-tender; the spleen was not palpable and there was no jaundice. A high serum cholesterol of 320 mgm. % was the sole abnormality of the liver function tests. Aspiration biopsy showed the picture of a marked degree of fatty vacuolation of liver cells.

CASE 5

PORTAL CIRRHOSIS

T.H., an emaciated male of 65 years, complained of nausea, vomiting, belching, and abdominal fullness for one week, with an aching pain in the epigastrium extending into the back and aggravated by food. He had lost 30 lb. in weight in the past year. His father had

died of bronchogenic carcinoma and his mother of carcinoma of the uterus.

Weakness, epigastric tenderness and enlarged liver, with a firm, nodular and slightly tender border were found. The blood sedimentation rate was 60 mm./hr. A large gastric ulcer was visualized on the lesser curvature. Laboratory tests showed serum bilirubin 0.98 mgm. %, serum protein 7.3%, A/G ratio 0.64. Bromsulphalein retention 20.2% after 30 min. Cephalin cholesterol flocculation plus two.

The clinical diagnosis was gastric carcinoma with hepatic metastases but needle biopsy of the liver showed a typical portal cirrhosis. Hepatic parenchyma was divided by large bands of fibrous tissue into small, false lobules. The fibrous tissue was dense, vascular, contained numerous bile ducts and many inflammatory cells.

*Other lesions.*—In a miscellaneous group of diseases, liver biopsy may be of use in visualizing the mechanism of hepatic enlargements. Two cases of lymphosarcoma showed a liver containing relatively large and diffuse masses of tumour. In a monocytic leukæmia, the liver sinusoids were filled with immature monocytes. Hæmochromatosis was diagnosed from liver cells laden with iron-containing pigment, which diagnosis was changed a year later to hæmosiderosis, lacking development of cirrhosis, diabetes or bronzing. An early case of cholangitis and biliary cirrhosis was disclosed and progress followed by repeated biopsies.

#### DISCUSSION

The use of this simple surgical technique has clear advantages in correlating the anatomical picture of the liver with the physiological and biochemical processes. The interpretation of so small a tissue section is open to doubt. The pathologist is faced with a minute core of liver which may course across several lobules but fail to give any complete architectural unit. The interpretation is made on a composite picture built up of small sectors of many lobules. A liver of normal consistence will yield a slender core of two or more centimetres in length which should give a fairly comprehensive picture. A liver toughened by portal cirrhosis, biliary thickening and scirrhous carcinoma, or, on the other hand, softened by necrotic changes, gives small broken fragments of tissue which add to the difficulty of technique and of interpretation.

Of the necessity and the safety of the procedure, there may be some criticism. With preliminary precautions indicated above, no reactions or complications of any severity occurred in our series. Chills with pyrexia of short duration was encountered once. Slight

upper abdominal splinting for a few hours was common, probably peritoneal reaction to a small plaque of fibrin and blood, plugging the puncture in the liver.

With regard to the clinical uses, we feel there are real advantages. In jaundice, an early liver biopsy has proved an almost infallible differential diagnostic procedure. In uncomplicated jaundice, a careful history and physical examination combined with selected biochemical tests rarely fail to provide a confident diagnosis and a biopsy may not be justified. But the histological picture may reveal obscure and unsuspected features, such as we found; namely cirrhosis, primary and secondary carcinoma and sarcoma, hæmosiderosis, and parenchymal changes secondary to obstruction.

In assessing the prognosis of hepatitis and portal cirrhosis, liver biopsy has proved a valuable aid. In these conditions, the correlation between liver function tests and hepatic histology has been very meagre<sup>5</sup> but our predictions of short term prognosis on the basis of biopsy have proved reasonably accurate. The ideal goal is the long term prognosis, the recognition of the indolent case of hepatitis which may progress to cirrhosis and further to portal or biliary obstruction.

As a control to various research and therapeutic measures, notably in fatty change or portal cirrhosis, liver biopsy has been found of value. In deciding on use or discontinuance of expensive medication and extra food factors, it is useful to follow the progress of treatment by histological control. It should find a special place in the consideration of operative treatment of Banti's syndrome. Liver damage from such hepatotoxins as chloroform, phosphorus and benzene derivatives may be estimated from biopsy. In a diffuse process in the liver, biopsy will give a fairly comprehensive picture. In a patchy or nodular process, however, such as secondary carcinoma, the aspirating needle may miss the lesions and lead to a false negative report. Evaluation of liver function tests is more comprehensive if correlated with the histological picture in the liver and an extensive investigation along these lines is presently being conducted in this hospital.\*

\* Since this paper was submitted for publication (September, 1948) the report of the investigation has been published in this Journal, Baird, M. M., Badre, E. J., Bogoch, A. and Maxwell, I. D.: *Canad. M. A. J.*, 61: 107, 1949.

### SUMMARY

Some indications for needle biopsy of the liver have been presented with mention of the possible dangers and a description of the technique employed.

The results in 75 such biopsies have been reviewed briefly, with more detailed account of the findings in five cases, infectious hepatitis, obstructive jaundice, secondary carcinoma, portal cirrhosis, and fatty liver, with mention of other conditions disclosed, namely lymphosarcoma, leukæmia, hæmosiderosis and cholangitis.

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## RHEUMATOID ARTHRITIS: RESULTS OF TREATMENT WITH DESOXYCORTICOSTERONE ACETATE AND ASCORBIC ACID (ARTHRODOX)\*

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THE dramatic response of some of the rheumatic diseases to cortisone has naturally led to an intensive search for other allied substances which would be equally effective and available at less cost.

The report of Lewin and Wassén,<sup>1</sup> which was quickly followed by that of LeVay and Loxton,<sup>2</sup> claimed that, in a majority of patients suffering from rheumatoid arthritis, a dramatic decrease in pain and stiffness followed the parenteral administration of desoxycorticosterone acetate and ascorbic acid. Ten subsequent short reports have given rise to considerable controversy since five<sup>3 to 7</sup> of them seemed to confirm the observations of Lewin and Wassén, whereas the others,<sup>8 to 12</sup> using the same technique, reported no significant response.

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In the following study, 37 patients with rheumatoid arthritis, 10 patients with ankylosing (Marie-Strümpell) spondylitis, and 3 patients with acute gouty arthritis were treated by the intramuscular administration of desoxycorticosterone acetate and ascorbic acid combined in a single ampoule (Arthrodox\*). Twenty-five of the patients (22 rheumatoid arthritis and 3 ankylosing spondylitis) were treated in hospital. The other 25 (15 with rheumatoid arthritis, 7 with ankylosing spondylitis and 3 with gouty arthritis) were treated as out-patients. All the patients were suffering from active disease and had been under observation for periods of months to years, their disease activity being relatively stable. The disability in the rheumatoid group ranged from Stage II to IV, Class II to IV as defined by the Committee on Therapeutic Criteria of the American Rheumatism Association.<sup>13</sup>

The 25 patients in hospital were first given control intramuscular injections of normal saline for three to five days prior to the administration of the drug. They were given two intramuscular injections of "arthrodox" each day—a total daily dose of 5 mgm. of desoxycorticosterone acetate and 1,000 mgm. of ascorbic acid—for a period of seven to fourteen days. Two of these patients were subsequently given cortisone.

In view of the startling results reported following one or two injections of desoxycorticosterone acetate and ascorbic acid,<sup>1, 2</sup> the 25 out-patients were treated with from one to six injections of "arthrodox". This group received no previous control injections.

A careful attempt was made to assess pain, stiffness, swelling, tenderness, range of movement of the joints, ability to rise from a chair, walk, turn in bed, etc. The patients' weight, appetite, sleep habits, requirements for sedatives, and general feeling of well being were noted.

### RESULTS

1. CLINICAL.—*Rheumatoid arthritis and ankylosing spondylitis.*—The first three patients treated were uncontrolled, and the first injection of desoxycorticosterone acetate and ascorbic acid appeared to give dramatic relief from pain and stiffness. Later studies, however, revealed that the administration of the combined drugs to 47

\* The material used in this investigation was generously supplied by Intra Medical Products, Toronto.