Effects of SC 1950 (2,6 Dimethyl Diethyl Piperidinium Bromide) on Peripheral Circulation.* (17701)

TRAVIS WINSOR.

From the Department of Medicine, University of Southern California Medical School, and the Nash Cardiovascular Foundation, Hospital of the Good Samaritan, Los Angeles, California.

Stimulation of the peripheral circulation is of decided benefit in the treatment of a number of clinical conditions, especially Raynaud's disease, reflex sympathetic dystrophy, and vasospasm accompanying arteriosclerosis obliterans as well as thromboangiitis obliterans. Such an increase in the blood flow to the extremities can be accomplished through medication with vasodilating drugs, however always at the risk of certain undesirable side reactions, as for instance, sleepiness, or dizziness. It was therefore decided to determine whether or not the new quaternary amine 2,6 dimethyl diethyl piperidinium bromide (SC 1950),† synthesized by I. C. Winter and his associates, increases the blood flow to the extremities and thus exerts a significant influence upon peripheral circulation. This drug, described as a ganglionic blocking agent, has proved in animal experiments to be several times as potent as tetraethylammonium bromide(1) and results in man and dog in lowering of blood pressure, reduction of tonus, and concomitant increase in the skin temperature of the toe(2).

Methods and materials. The effectiveness of SC 1950 was studied in 5 normal individuals and 21 patients with peripheral arterial disease. Of the normal individuals, 3 were males, 2 females, the average age in this group amounting to 28 years (21 to 42). Of the 21 patients with arterial disease, 14 were males, 7 females, the average age in this group amounting to 33 years (24 to 55). In 10 cases the diagnosis was arteriosclerosis obliterans, in 5 essential benign hypertension, in 4 thromboangiitis obliterans, while hypertension secondary to pyelonephritis, and to periarteritis nodosa was noted in one case each. The experiments were conducted under standard reproducible conditions. All subjects were dressed in hospital gowns and examined after 45 minutes of rest. Observations were made in an air conditioned room with a temperature of 25°C ± 1.5°, the air velocity amounting ordinarily to less than 10 feet per minute.

Changes in the volume of the extremities were determined by means of a digital pneumoplethysmograph(3) and a digital cup was fastened to the tip of the right or left second toe or finger. Plethysmograms were standardized so that volume changes were recorded in cu mm/5 cc per sec. Blood flow to the extremities was ascertained through venous occlusion(4) and a collecting cuff placed at ankle or wrist and in selected cases at finger or toe. In order to establish the skin temperature, thermocouple junctions were fixed to the skin of the extremities with cellulose tape, and readings from a 12-point electronic potentiometer were recorded every 15 seconds. These observations were exact within ± 0.25°C, and the accuracy of the instrument employed was frequently tested with a National Bureau of Standards mercury thermometer, exact to within 0.1°C. Blood pressure was measured by the standard auscultatory or the plethysmographic method, or in

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† Drug gratuitously provided by the Research Laboratories of G. D. Searle and Co.

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selected cases additional continuous tracings were taken using the Sphygmotonograph(5). Oscillometric readings were recorded by means of the Collen's Sphygmo-oscillometer. The cardiac rate was calculated from the plethysmogram. As a rule, SC 1950 was administered through an intravenous tube by slow injection over a period of 15 minutes and in a dose of one-half mg per kg of body weight. Control determinations were made with normal saline introduced by intravenous drip at the rate of 10 drops per minute.

Results: Effect of SC 1950 on Blood Pressure, Pulse Rate and Respiratory Rate. Blood pressure was consistently lowered in normal individuals as well as in patients with early or advanced peripheral arterial disease. Among normal individuals the blood pressure dropped from an average of 132/80 (118/76 to 140/90) before injection to 85/63 (60/40 to 100/68) 25 minutes after instillation of SC 1950. Consequently the pulse pressure fell from an average of 52 mm Hg before to 22 mm Hg, 25 minutes after injection. In 2 normal individuals 40 mg were administered in 3 minutes and the blood pressure reached its lowest level within 8 minutes; injection extending over a period of 15 minutes, on the other hand, resulted in a less pronounced fall of pressure. The hypotensive state lasted for a variable period of time, the average for the entire group of 26 subjects amounting to 55 minutes. The three normal individuals, however, showed lowered blood pressure readings for more than 150 minutes. In patients with hypertension and obliterative arterial disease the blood pressure was also lowered by the drug. However, the response of patients of this type to comparable doses showed considerable variations and necessitated great care in the administration of SC 1950. For instance, in the case of a patient with essential benign hypertension the blood pressure fell from 180/100 before injection to 70/60 following administration of 40 mg of the drug. The patient became ashen gray and complained of precordial pressure, but 10 minutes after arms and legs had been elevated the blood pressure returned to 100/70. As the patient's renal function, determined by clearance and phenolsulfonphthalein tests proved to be normal, his unusual sensitivity is not readily explained.

In normal individuals (Fig. 1) as well as in patients with peripheral arterial disease the Flack test gave ordinarily positive values as long as the blood pressure was reduced, similarly as in Hecht and Anderson's study on dibenamine(6); however, the Flack test turned negative as soon as the blood pressure once again reached a normal level. Postural hypotension appeared generally a few minutes after completion of injection, but became less marked when the blood pressure began to return to normal. The pulse rate ordinarily was accelerated following intravenous injection of SC 1950. In 3 of the 5 normal individuals the pulse rate increased from an average of 102 (80 to 134) before injection, to 132 (92 to 148) within 10 minutes after injection. With the return of the blood pressure to normal, the pulse rate reverted to its pre-injection level. In patients with arteriosclerosis obliterans or with essential hypertension the pulse rate showed generally little change following injection of the drug. This obvious dissimilarity in the response to SC 1950 may well have to be explained on the basis of varying degrees of blocking of the autonomic nervous system obtained in different individuals.

The respiratory rate was studied in all 26 subjects, and 9 times no significant change was noted; in the remaining 17 cases respirations became shallow following administration of SC 1950, most noticeably so in conjunction with a marked decline in blood pressure.

Effect of SC 1950 on Pulsations of Extremities and Digits. In the 5 normal individuals the pulse volume of the digit showed a marked increase under the influence of SC 1950. A fair rise in pulse volume is ordinarily encountered in patients with moderate peripheral arterial disease, and in one typical case in that group (Fig. 2) the pulse volume rose within 15 minutes from 0.2 cu mm/5 cc of tissue to 4.0 cu mm. Among patients with advanced

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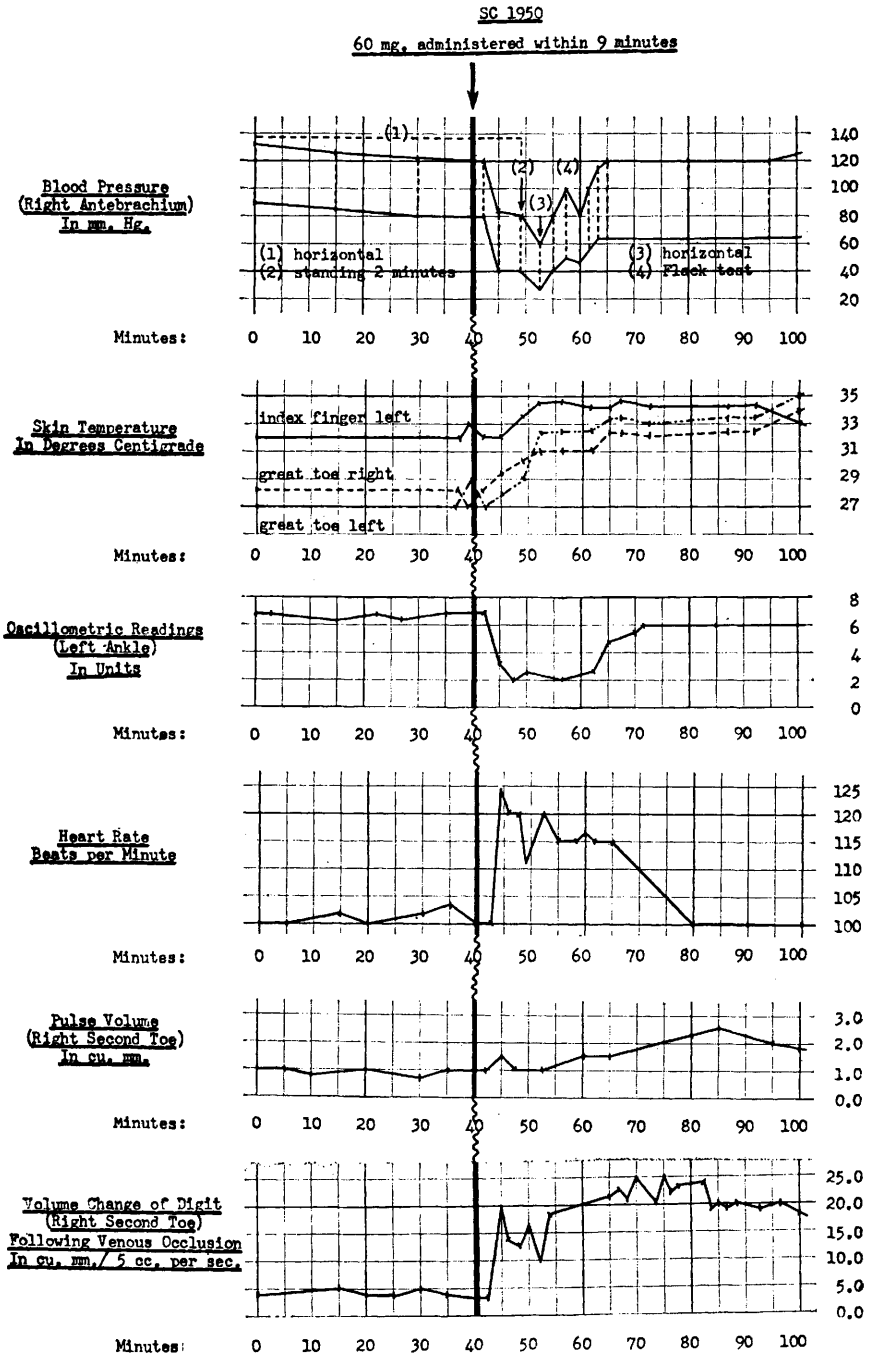

FIG. 1.

Effect of SC 1950 on peripheral circulation in normal male, age 32. Definite fall in antebrachial blood pressure to a hypotensive level, with postural hypotension as well as positive Flack test 17 min. after intravenous inj. of 60 mg SC 1950. The skin temp. of dorsum of left toe increased in 60 min. from 27.1 to 34.0°C. Oscillometric readings showed a decided fall. The heart rate rose sharply during the hypotensive phase. Amplitude of pulsations in the toe was accentuated as blood pressure returned to normal. Volume change following venous occlusion (relative toe flow) increased about 8 times.

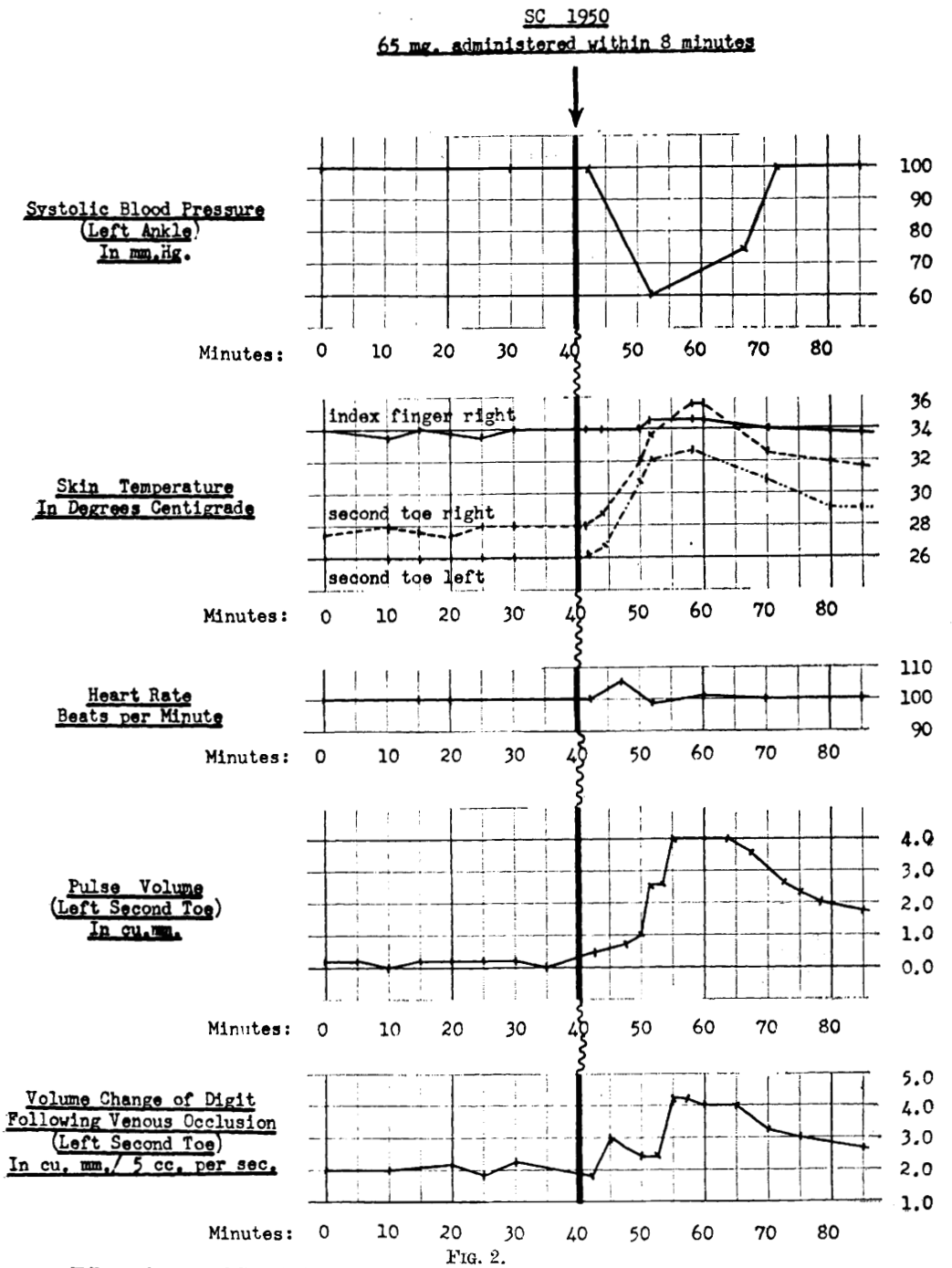

FIG. 2.

Effect of 65 mg SC 1950 intravenously, on peripheral circulation of a 34 year old male with early thromboangiitis obliterans of left leg. Pain in left calf on walking 4 blocks. Following inj., systolic blood pressure at left ankle fell 40 mm Hg. Skin temp. in left toe increased less than in the right. Heart rate slightly accelerated. Pulse vol. rose noticeably. Volume change following venous occlusion (relative toe flow) moderately increased.

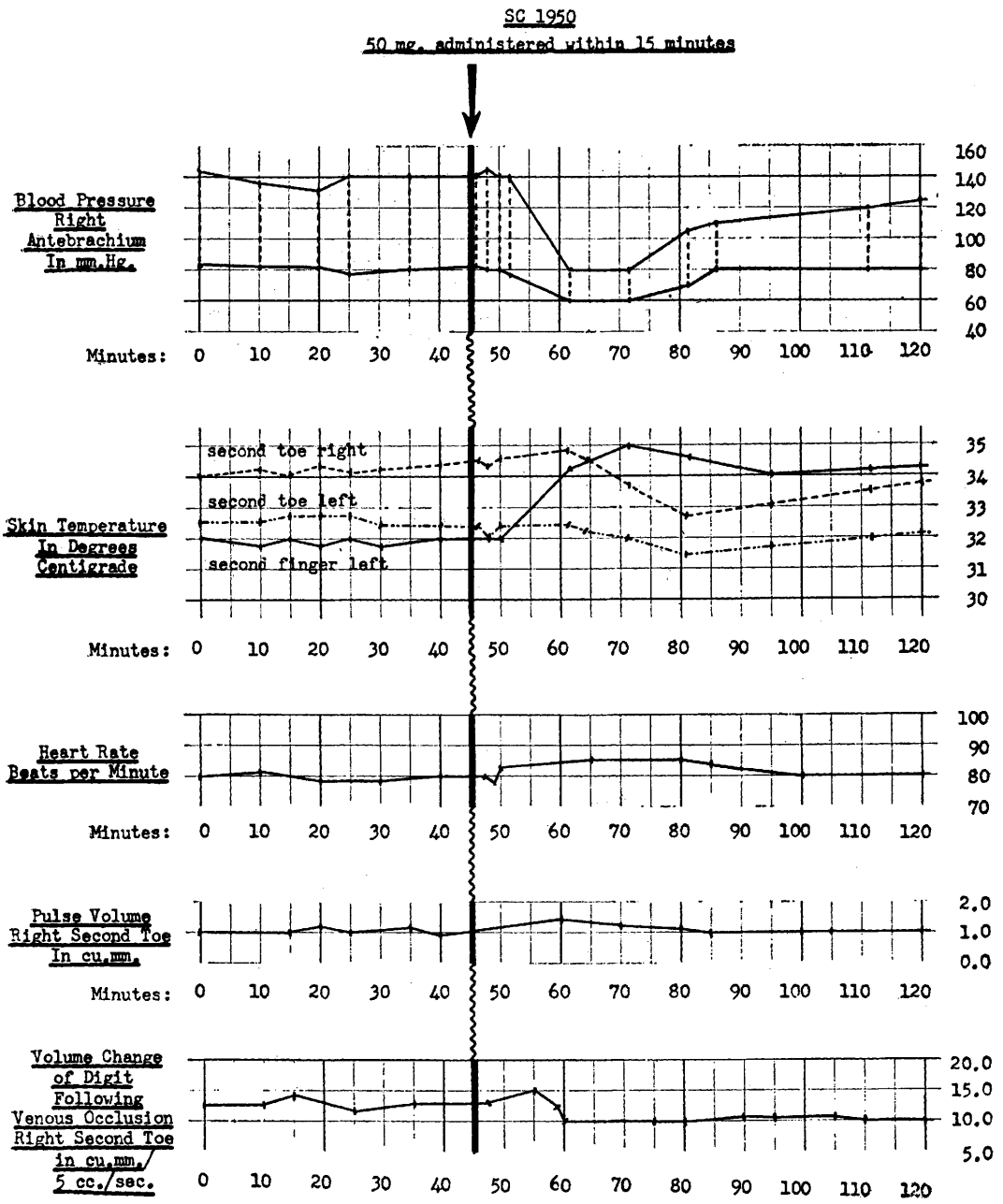

FIG. 3.

Effect of 50 mg SC 1950 intravenously, in 55-year-old male with arteriosclerosis obliterans and polycythemia. Pain in calves upon walking 2 blocks. Hypotensive effect lasted in excess of 55 min. Slight decline in skin temp. of toes may be due to shunting away of blood from diseased lower extremities to more normal parts of body, *i.e.*, second left finger, in which skin temp. was elevated. Heart rate increased slightly, perhaps due to blocking of para-sympathetic nervous system. Pulse vol. changed insignificantly probably on account of arteriosclerotic obliterative disease of peripheral arteries. Vol. change following venous occlusion (relative toe flow) only momentarily higher, then declined somewhat, due to shunting away of blood.

peripheral arterial disease the digital pulse volume increased only insignificantly. (Fig. 3).

Oscillometric readings recorded at the brachium were carried out in a group of 10 in-

dividuals composed of normal subjects as well as of patients with peripheral arterial disease. Pulsations in the arteries declined from an average of 7 units (3 to 12) before injection to 3 units (1 to 7.5) ten minutes after administration of the drug. As in 2 patients marked lowering of the height of pulsations was not accompanied by any significant increase in blood flow or skin temperature, this finding will most likely have to be traced to decreased cardiac output.

Effect of SC 1950 on Digital Blood Flow and Skin Temperatures. Administration of SC 1950 in normal individuals led to a marked increase in the blood flow to the toe. In a specific case (Fig. 1) the relative toe flow rose from 3.0 cu mm/5 cc per sec. to 25.0 cu mm, as compared with a value of 20.0 cu mm, obtained after release of 5 minutes arterial occlusion above the knee. The skin temperature rose 7°C in each toe. In the same subject body heating, using 2 woolen blankets as well as 2 electric pads for a period of 40 minutes, resulted in an increase in digital flow amounting to 30.0 cu mm/5 cc per sec. In patients with mild peripheral arterial disease, an increase in blood flow to the extremities as well as a rise in the skin temperature was observed upon intravenous instillation of the drug, but the readings always remained decidedly below normal levels. For instance, in a case of early thromboangiitis obliterans of the left leg (Fig. 2) flow to the left toe increased following injection from 2.0 cu mm/5 cc per sec. to 4.5 cu mm. Five minutes after release of arterial occlusion the toe flow reached 5.0 cu mm/5 cc per sec. Under the influence of SC 1950 the skin temperature of the left second toe rose from 26.0° to 32.8°C, a value well below normal, but very similar to the reading of 33.2°C obtained after 40 minutes of body heating. In the presence of advanced peripheral vascular disease neither the digital blood flow nor skin temperature was significantly influenced by administration of SC 1950. A patient with arteriosclerosis obliterans and polycythemia, for instance, (Fig. 3) showed a rise in peripheral flow from 12.0 cu mm to 16.0 cu mm/5 cc per sec., while following release of 5 minutes arterial occlusion it amounted to 9.0 cu mm. Skin temperature of the toes increased only slightly in the right second toe from 34.0° to 34.8°C.

Vasomotor Reactions and Side Effects. SC 1950 was furthermore studied as to its possible influence upon the variations in the amplitude of pulse waves as well as in the volume of the digit normally produced through respiration. The 5 normal subjects were examined at 2 minute intervals before and 15 minutes after injection of the drug. Before injection all 5 subjects presented upon sharp thoracic inspiration the normal decrease in the amplitude of pulse waves as well as in digital volume. Following injection of SC 1950 a definitely changed pattern could be observed. Either no reaction whatever appeared upon inspiration, or an increase in the volume of the digit occurred as a paradoxical response. Both effects were taken to indicate that satisfactory blocking of the sympathetic nervous system had taken place.

Side reactions were relatively common and occurred in one-fourth of the 26 subjects. These responses included nasal obstruction, sighing inspiration, weakness, nausea, dizziness, sleepiness, restlessness, angina, dry mouth, swelling of the throat, heavy eyelids, visual disturbance, and thick speech. When SC 1950 was administered rectally as a retention enema in a dose of 25 mg per kg of body weight, the same changes in blood pressure as following intravenous injection were observed, but there occurred also the identical side reactions.

Summary and conclusions. SC 1950 has a profound effect on the peripheral circulation. A fall of blood pressure is observed in normal individuals as well as in patients with peripheral vascular disease, but in the latter group this response is subject to considerable variations. The pulse rate is frequently elevated, and considerable variations occur following intravenous injection of SC 1950. The pulse volume of the digits shows a marked increase in normal individuals, is somewhat less in patients with moderate peripheral arterial disease, and varies only insignificantly in patients with advanced organic peripheral arterial disease. In normal individuals the skin temperature of the digits rises sharply, often

as much as 8°C, while little change is observed in patients with advanced peripheral disease. Digital blood flow in normal individuals shows a marked increase, while it rises only slightly in patients with moderate or advanced peripheral arterial disease. In all groups the fall in systolic pressure is greater than that in diastolic pressure. From these observations it may be concluded that SC 1950 is an effective spasmolytic agent, capable of increasing the blood flow to the periphery, but beset by a number of side reactions upon intravenous as well as rectal administration.

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Adsorption, Distribution and Excretion of Tripelennamine (Pyribenzamine). (17702)

E. LEONG WAY* AND ROBERT E. DAILEY.†

From the Department of Pharmacology, George Washington University, School of Medicine, Washington, D.C., the College of Pharmacy and the Division of Pharmacology, School of Medicine of the University of California, San Francisco.

Despite the wide therapeutic usage of tripelennamine (Pyribenzamine), little is known in regard to the physiological disposition of this antihistaminic agent. The urinary excretion of tripelennamine after oral administration has been reported to be about 10%(1), 15.8-25.5%(2), and greater than 85%(3). So far as we have been able to ascertain, the tissue distribution of this compound has not been reported. Our interest in general in the metabolism of basic amines of therapeutic interest led us to investigate the absorption, distribution, and excretion of tripelennamine.

Procedure and results. Estimation of tripelennamine. This was accomplished by applying a general procedure for organic bases described by Brodie and Udenfriend(4,5). The method is based upon the extraction of the base from tissue brei with an organic solvent and then reacting the compound with methyl orange to form a colored complex which is soluble in the solvent and can be measured photometrically. Technical grade benzene was found to be a suitable solvent for quantitatively extracting tripelennamine from tissues. Low blanks (optical density less than 0.015) were obtained for most tissues.‡ A high degree of specificity for the method was attained by washing the benzene extract of tissue with 0.5 M phosphate buffer pH 7. This procedure resulted in the removal of a small amount of interfering material, presumably metabolic products of tripelennamine, which reacted as the parent compound.

To illustrate the specificity of the procedure the distribution ratios of tripelennamine between benzene and water at various pH values were compared with those of apparent tripelennamine recovered from tissue minces of rats given the compound. The results, as shown in Table I, indicate that the method is highly specific since the distribution ratios of the recovered drug are in good agreement with those of a known sample of tripelennamine.

* Present address: University of California, Medical Center, San Francisco, Calif.

† Present address: Smith, Kline, and French Laboratories, Philadelphia, Pa.

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‡ Technical benzene on standing may give higher brain blanks and must be checked at frequent intervals for such changes. Also, brain blanks vary with different samples of technical benzene.