Table showing the Effect of Sympathetic Ramisection in Twenty-six Consecutive Cases of Spastic Paraplegia.

BEFORE OPERATION.									AFTER OPERATION.						
Case No.	Age.	Able to Sit Up.	Able to Stand Alone.	Able to Walk Alone.	Able to Walk with Support.	Able to Balance on one Limb.	Was Patient Constipated?	Mentality.	Stand- ing.	Walk- ing.	Balance on one Lower Limb.	Ease in Performing Active Movements.	Consti- pation.	Mental Con- dition.	Time in Months Since Operation.
1	14	+	-	-	-	-	+	-	+	+	+	+	+	+	35
2	6	-	-	-	-	-	++	?	++	+	+	++	++	...	9
3	13	+	+	+	+	-	++	+	++	++	++	+	++	...	4
4	23	+	+	-	+	-	+	?	+	+	++	++	-	+	14
5	5	-	-	-	-	-	+	?	+	+	+	+	+	...	17
6	27	+	+	+	+	?	+	-	-	-	-	-	-	-	28
7	5	+	-	-	-	-	-	+	+	+	+	++	...	...	14
8	38	+	+	+	+	-	-	+	+	+	+	+	...	...	6
9	11	-	-	-	-	-	-	-	-	-	+	+	...	+	20
10	31	+	+	+	+	-	-	-	+	+	+	+	...	+	21
11	7	+	-	-	-	-	+	-	+	+	+	++	++	+	20
12	12	+	-	-	-	-	+	-	+	+	-	+	...	+	17
13	19	+	+	+	+	-	-	+	+	+	++	+	...	+	33
14	14	+	+	+	+	-	-	+	+	+	+	+	...	...	14
15	3	+	-	-	-	-	+	+	+	+	+	+	+	...	4
16	11	+	-	+	+	-	+	+	+	+	+	+	+	...	9
17	3	+	-	-	-	-	+	+	+	+	+	+	?	...	30
18	17	+	+	+	+	-	-	+	+	+	+	++	...	...	18
19	15	+	-	-	-	-	+	?	+	++	++	++	+	+	36
20	30	+	+	+	+	-	-	+	+	+	+	+	...	...	7
21	15	+	+	-	+	-	+	-	+	+	+	+	+	...	30
22	23	+	-	-	-	-	+	+	+	++	++	++	+	...	21
23	14	+	-	-	-	-	+	-	+	+	+	+	+	+	18
24	15	+	+	-	+	-	+	+	+	+	+	+	+	...	17
25	9	+	+	+	+	-	+	-	++	++	+	+	+	...	1
26	19	?	-	-	-	-	-	+	++	++	++	+	-	+	9
		(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)	(10)	(11)	(12)	(13)	

Explanation of Signs Used in the Table.—In (1), (2), (3), (4), (5), and (6) the sign + signifies "Yes," the - sign "No." In (7) the + sign signifies normal mentality, the - sign signifies subnormal mentality, and the mark ? indicates mainly a defect through lack of education. The + sign in (8), (9), (10), (11), and (12) indicates the degree of improvement after operation. In (13) it indicates a noticeable improvement.

period; the Babinski test was doubtful. After a bilateral sympathetic ramisection there was an immediate change for the better in tone in the limbs operated on. Six weeks after the operation the patient was able to stand, and a few days later commenced to walk. Eight months after the operation she could stand unsupported for at least ten minutes and could walk alone for a hundred yards. The choreic movements have disappeared from the lower limbs when the patient is not excited, and there is some improvement in the upper limbs also.

Other cases which have been operated on are too recent to merit report.

In the concluding part of his paper Dr. Royle deals with the physical education of the spastic paralytic.

"It must," he says, "be clearly understood that the operation of sympathetic ramisection is not advocated as a cure for spastic paralysis. . . . It merely removes a factor which has been interfering with the normal physical education of the individual, and the essential treatment of spastic paralysis is education of the central nervous system. . . . It is true, however, that the treatment of paralysis of any variety has a peripheral as well as a central aspect, but in spastic paralysis the muscles themselves usually do not need attention; indeed, treatment with massage and electricity only tends to stimulate the sensory end-organs in the muscles, and this inevitably leads to an increase in tone. . . .

"It is sometimes thought that the operation of sympathetic ramisection should confer full and normal use of the muscles immediately, but this is a misconception. We can no more expect the subject of a congenital spastic paralysis to walk immediately after operation than we can a newborn infant. The normal child takes a year or longer to acquire control over the lower limbs sufficient to enable

it to walk, and a similar time must be allowed for the spastic child. . . . Even when movements can be performed voluntarily in the lower limbs, control of the various groups is imperfect and the first consideration in education is to establish group control.

"The minimizing of mental effort must next be aimed at. On account of the fact that the patient's muscles have always been opposed by the rigidity of their antagonistic muscles, his mental effort is exaggerated and this tends to the use of unnecessary muscles. This mental habit persists and must be counteracted by teaching inhibition in the groups whose contraction would render the given movement defective."

VASCULAR DISEASES AND THE SYMPATHETIC SYSTEM.

BY

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SIR W. I. DE C. WHEELER's¹ recent report on two cases of thrombo-angiitis obliterans calls attention to problems of great interest. It may be useful to give an account of what is being done by investigators working in the various departments of medical inquiry to interpret the significance of disease in the blood vessels and the part possibly played by the sympathetic nervous system in their causation. In his Oliver-Sharpey lectures Dale² gave an excellent summary of the history of our present knowledge,

with special reference to the capillary bed. After submitting Stricker's proof of the contractility of the capillaries, Mayer's proof of the nervous control of the capillaries by the sympathetic nervous system, and Hooker's proof of the nervous control even when the circulation is at a standstill, Dale gives a vivid account of the work of a long series of observers in relation to anaphylaxis and to histamine shock. He discusses the experiments of Ninian Bruce in relation to local vasodilator reflexes, and deals in detail with the work of the schools which have grown up around Krogh, Sir Thomas Lewis,³ and himself. From the historical point of view two incidents may be added. In 1850 Alfred Smee⁴ showed preparations of the capillaries of the brain, eye, muscle, and skin, injected with carmine size, and suggested that the variation in the quantity of blood in the capillaries influenced the position of the lens and so controlled accommodation. In 1860 Lionel Beale⁵ depicted fine non-medullated nerves coursing with the capillaries in striped muscle. Beale's researches in this connexion deserve special mention, for it is only recently that van den Bergh, McNee, and F. C. Mann have called attention to his brilliant work on the liver. Lionel Beale was "an inarticulate verbose genius" and a protagonist of the Vitalist School, "whose scientific observations were largely ignored as a result of the brilliantly lucid dialectic of Thomas Henry Huxley."

Dale expresses surprise that Rouget's demonstration, in 1873, of the contractile cells which bound the capillary endothelium should have remained unnoticed until comparatively recent times. The Rouget cells are flat contractile stellate cells applied to the outside of the capillary endothelium and encircling the vessel by delicate protoplasmic processes. That these cells had been observed before is evident from the description given by Eberth and Iwanoff in 1868⁶:

"As the capillaries become larger a delicate tunica adventitia is superadded, which . . . is formed of a delicate network of fine fibrils, composed of the processes of stellate cells lying directly on the vascular wall."

Mayer, Vimtrup, and Dale regard these cells as contractile, sympathetically innervated, and so controlling largely the quantity of blood in the capillary bed. Recently E. R. and E. L. Clark⁷ have shown that in the tadpole the capillaries display two types of contraction—the one with a wavy contour of the contracting small capillaries, and the other with a general reduction in the calibre of the larger capillaries. These contractions of the capillary are seen in young capillaries before any Rouget cells are attached thereto. During contraction the capillary is separated from the Rouget cell by a space which can be seen in a profile view. Hence the tonicity of the capillary endothelium of the amphibian larva is independent of the presence of the adventitial cells of Rouget. This finding of the Clarks is of great interest, inasmuch as fifty years ago Roy and Graham Brown said that the capillaries were elastic and contractile in themselves. Florey and Carleton,⁸ in a recent paper on the capillaries of the cat, state that they are in general agreement with this view, and that the presence of Rouget cells in sufficient numbers to account for the contraction is doubtful.

An entirely different approach to the question of the nervous control of the blood vessels may be seen in the anatomical school associated with Elliot Smith.⁹ His description in 1895 of a branch of the external thoracic nerve supplying the axillary artery, in conjunction with the late Sir William Thorburn's interest in cervical rib, led Todd¹⁰ to a study of the effect of nerve lesions on the arteries. The observations of Wood Jones¹¹ on the relation of the nerve trunks to the uppermost ribs had also directed particular attention to this problem. Most of this work centred around the endarteritis obliterans which is seen in certain cases of cervical rib. Buzzard,¹² in 1902, was the first to suggest a vascular causation of the trophic disturbances seen in cases of this condition. He stressed the absence of herpes and papillary symptoms in the upper limb, and so concluded that the trophic disturbances were due to a lesion of the first thoracic nerve between the junction of the anterior and posterior roots and its union with the eighth cervical nerve to form the lower trunk. He regarded the spinal nerve itself as the seat of the

change. Todd suggested that the trophic lesions of cervical rib were due to a lesion of the sympathetic nerves which run from the first (and sometimes the second) thoracic ganglion to course over the cervical rib on the under side of the lowest trunk.

Numerous papers were published in relation to the vascular symptoms of cervical rib by Todd, Telford, Wood Jones, and others. In 1914 Todd and Kramer¹³ surveyed the distribution of nerves to the arteries of the arm. They showed that the subclavian and axillary arteries differ from the other arteries of the arm in receiving a nerve supply direct from the sympathetic chain. All other arteries in the upper limb obtain their nerve supply from sympathetic filaments which have travelled along the spinal nerves and are distributed to the various blood vessels at irregular intervals. The distal and peripheral blood vessels, more particularly those of the hand, receive nerve filaments at more frequent intervals than do the proximal channels. The distribution of nerves to vessels thus corresponds roughly with the distribution of nerves to the muscles and skin. The process of the blood vessel affection appears to be a preliminary period of stimulation of the sympathetic vaso-constrictor fibres followed by a paralysis of the vaso-constrictor fibres with consequent changes in the vessel wall. In short, the trophic lesions are the result, not the cause, of the vascular lesion.

A considerable amount of experimental work has been done in a direction which closely reproduces the trophic lesions of cervical rib. Bechterew summarized the results in 1908, and particular mention must be made of some of the experiments. Lapinski cut the cervical sympathetic in rabbits and showed that the arteries of the ear presented endarteritis obliterans, fragmentation of the elastic coat, and hyperplasia of the tunica media. This was followed by a rapid patchy atrophy of the media. These results were obtained in only seven out of fourteen animals. Cehanovič repeated these experiments, and demonstrated a lack of tone and a delay in the pulse wave in the arteries comparable to that seen in human arterial disease. Fraenkel cut the sciatic nerve in rabbits and dogs and obtained lesions which closely resembled those seen in the anterior tibial vessels in tabes. This was confirmed by Bervoetz. Cyzharz and Helbing repeated these experiments, but did not obtain the vascular changes in all cases. Subsequent to the operation certain rabbits exhibited trophic changes in the dorsum of the foot, and in these alone were found the typical pathological changes in the vessels.

Had the correlation between anatomy and physiology been sufficiently close these experiments would have been readily interpreted. Schiff,¹⁴ in 1854, showed that, allowing an interval of ten days for degeneration, excision of the superior cervical ganglion and of the upper part of the cervical sympathetic trunk did not prevent the vaso-constriction which he was the first to observe in stimulating the great auricular nerve. So Schiff concluded that the vaso-constrictor fibres of the great auricular nerve arise from the spinal cord in the upper cervical region and pass outwards in the roots of the second and third cervical nerves, which send branches to the great auricular nerve. These experiments were not confirmed until over forty years later, when Morley Fletcher¹⁵ repeated them, and showed that some of the sympathetic fibres which reach the ear do so by the ramus vertebralis of the ganglion stellatum, along the vertebral artery to the third cervical nerve, and thence by way of the great auricular. It now became obvious that the discrepancies in the results obtained in the vessels by section of the sciatic nerve were due to the fact that some of the sympathetic fibres reach the lower limb along the femoral artery. Thus in each case the vessels of the limb receive a dual supply of sympathetic fibres—first, from the nerve plexus on the aorta and large vessels, and secondly, from the mixed peripheral nerve.

One of the first clinical applications of this was seen in the work of Leriche, Policard,¹⁶ and their associates. They showed that the mechanical stimulation of the periarterial sympathetic plexus led to vaso-constriction, and that removal of the plexus led to a favourable vaso-dilatation in cases of trophic disturbance. They showed that the reaction of the periarterial sympathetic network varies in degree,

being more marked in some animals, less in others. It is more evident in the brachial than in the axillary or subclavian arteries, more active in the femoral than in the iliac arteries, in the brachial even more than in the femoral. The operative procedure of Leriche has not been taken up with enthusiasm in this country. However, Shaw¹⁷ states that periarterial sympathectomy has been successful in 75 per cent. of cases of causalgia in the clinics of Leriche and Platon. Langley¹⁸ says periarterial sympathectomy in man, so far as it relieves peripheral vaso-constriction, in all probability does not do so by severing nerve fibres running with the arteries to the periphery. Stopford¹⁹ has discussed the possible nerve mechanism in cases of causalgia, and is inclined to consider that the main factor is a reflex peripheral vaso-dilatation of the vessels.

Recently Woollard,²⁰ in the Institute of Anatomy, University College, London, has confirmed the view that the limb vessels are innervated proximally by nerves direct from the aortic plexus and distally by contributions from the adjacent mixed nerves. Medullated nerves are shown most abundantly on the peripheral vessels, and they end not only by collaterals on the vessels, but also in the adjacent tissues. Woollard suggests that this anatomical relationship may be the basis of the axon reflex. He confirmed the sympathetic innervation of the capillaries, and shows sensory nerve endings of medullated fibres on the large, medium, and small arteries.

The whole problem of a sympathetic afferent apparatus is still in doubt. Trotter²¹ has put forward the view that all naked nerve endings register pain, and that pain is the primordial mode of sensation. From it the discriminative forms of sensibility have been differentiated by the progressive degree of insulation of the nerve fibre, which is indicated by the acquirement of a medullated sheath on the one hand and by a special type of nerve ending on the other. Both in the preparations of Kulchitsky²² and in those of Woollard one is struck by the number of naked non-medullated fibres which wander out into the tissues to form "free" endings.

A different point of view has emerged from the work of Pavlov²³ and Orbeli.²⁴ Briefly one might say that the Leningrad school of physiology is gradually establishing the existence of the trophic fibres which were empirically postulated by the ancient surgeons. Orbeli regards the sympathetic as containing fibres which regulate the somatic sensory and motor nerves, and determine the amount of material used in each tissue in the body. This work, largely unpublished, cannot be discussed in detail at present. It is mentioned in particular to call attention to the tendency to extend the range of sympathetic innervation to all the tissues in the body.

A tremendous impetus to the study of the sympathetic system followed the revolutionary publications of N. D. Royle²⁵ and the late John Irvine Hunter.²⁶ It is not proposed to discuss their application of sympathectomy to spastic paraplegia and allied conditions, but to indicate one result of the revival of the interest in the sympathetic system. The surgery of this system is not new. Nearly all the early operations have been discarded. The value of the few that have survived is still equivocal; and many have produced either indifference or bitter opposition. In 1889 Alexander²⁷ of Edinburgh resected the superior cervical ganglion of both sides; in 1892 Jacksh²⁸ resected the vertebral plexus and cut the cord connecting the middle and inferior ganglion; in 1893 Bojdanik²⁹ performed bilateral resection of the middle cervical ganglion; and in 1896 Jaboulay³⁰ cut the sympathetic cord above and below the ganglion. All of these operations were done for epilepsy. Jaboulay performed sympathectomy for exophthalmic goitre in the same year, and Jonnesco³¹ performed the operation for glaucoma in 1897. Ball³² of St. Louis, in 1899, removed the superior cervical ganglion for optic nerve atrophy and for glaucoma.

One outcome of the work of Hunter and Royle has been the rapid application of sympathectomy to diseases of the vasomotor apparatus. Adson³³ of Rochester noticed that, following removal of the second, third, and fourth lumbar ganglia in a case of spastic paraplegia, striking and persistent vaso-dilatation occurred in the feet for a period of

six weeks. The vaso-dilatation was uniform and uninterrupted, and the feet became hot and dry with suppression of visible sweating. Adson and Brown³⁴ have published a series of papers dealing with the peripheral vascular disturbances of the extremities. In Raynaud's disease periarterial stripping gives no relief, but combined with lumbar sympathectomy it does. Cervical sympathectomy also causes marked relief when performed alone. In cases of endarteritis obliterans stripping of the vessels, as opposed to the results of some other surgeons, has given no relief. The injection of a foreign protein (typhoid vaccine) has relieved the symptoms in 50 per cent. of the cases, but sympathectomy has not been tried owing to the wide distribution of the concomitant arterio-sclerosis. In thrombo-angiitis obliterans occasional relief from pain has been obtained by the intravenous injection of foreign protein and by Roentgen-ray irradiation of the spine. Lumbar sympathectomy combined with stripping of the external iliac arteries has given marked relief from pain, the condition of the limb has improved, and trophic ulcers have healed. The heat evolution of the limb has increased from 50 to 110 per cent. and the temperature of the limb has increased from 1.5° to 6.4° C. These measurements were made with Sheard's thermo-couple thermometer and foot calorimeter. The results of sympathectomy in erythromelalgia have not yet been ascertained, but medical treatment and surgical stripping of the vessels have not availed.

The work of the surgeons in the Mayo Clinic is interesting in that, first, the thermal response to the injection of a foreign protein gives a ready indication of the degree of suitability for operation in a given case of vascular disease, and that, secondly, the results of sympathectomy in Raynaud's disease and in thrombo-angiitis obliterans are remarkably promising even after an interval of six months. The pain of thrombo-angiitis obliterans is extreme, sleep is fitful, and the patient is rapidly reduced to a mental and physical wreck. Even if such an operation postpones amputation for a few months its performance seems to be justified.

A further dramatic application of the operation of lumbar sympathectomy was witnessed in the following case.

The patient, a woman, aged 34, whose limbs were crippled with a polyarthritis of the rheumatoid type, had failed to respond to medical treatment over a period of six years. The hands and feet were cold and moist with trophic changes in the skin and nails; the interphalangeal joints were all enlarged and there was typical spindle-shaped swelling of the middle and index fingers. There was 25 per cent. limitation of movement in the ankles, 30 per cent. in the wrists, 20 per cent. in the elbows, and 50 per cent. in the shoulders. Pain was a prominent symptom in the hands and feet. As a result of the hopeless condition of the patient bilateral lumbar sympathectomy was suggested by Dr. Rowntree³⁵ and performed by Dr. Adson. The heat emitted from the feet was increased by 100 per cent. and the temperature by 8° C. I saw the patient before and after operation. The feet became warm, dry, and pink; the trophic changes in the skin and nails were disappearing. Pain had disappeared entirely from the feet and there was a sense of warmth therein. The patient was able to walk several hundred yards within five weeks of the operation. She is a typist, and has requested bilateral cervical sympathectomy, but it was deemed well to wait for six months or a year.

The effect of the operation in this case is equivalent in some respects to a particularly persistent passive hyperaemia of Bier, and one of the treatments employed in the Mayo Clinic in trophic conditions of the hands and feet is the application of an electrically heated glove or sock such as is worn by our Royal Air Force pilots at high altitudes.

Whereas Adson had been a champion of the Hunter-Royle operation for selected cases of spastic paraplegia, the Chicago surgeons Kanavel and Davies have strongly denied its benefits. It is gratifying, therefore, to see Davies and Kanavel³⁶ adopting lumbar and cervical sympathectomy for cases of vascular disease. They report marked relief of the symptoms of Raynaud's disease after cervical sympathectomy, marked relief of erythromelalgia by lumbar sympathectomy, and complete failure to obtain relief in a case of thrombo-angiitis obliterans. Their conclusions differ from those of Adson and Brown in that the latter operate for thrombo-angiitis obliterans, but not for erythromelalgia. I am tempted to suggest that the case of erythromelalgia might have been an early case of thrombo-angiitis obliterans. The patient was a Russian

Jewish tailor, aged 35. It is true that the arteries of both legs and feet were easily palpable in this case, but the disease may be more marked on the venous side of the capillaries in the earlier stages and limited, like many cases of post-operative thrombosis, to the deep veins of the calf. Pain is often more marked in the calf than in the foot, and is a phenomenon of veins as well as of arteries.

Wheeler's¹ two cases, and the two cases simultaneously published by Smith and Patterson,² along with the fact that Telford and Stopford³ saw four cases in one year in non-Jewish patients, suggest that great care is necessary for the accurate differential diagnosis of the various types of vascular disease of the extremities. It is not sufficient to say "threatened gangrene"—nor, for that matter, is "erythromelalgia" more than a symptom.

Stopford has mentioned that the clinical characters of thrombo-angiitis obliterans were first described by von Winiwarter in 1879, long before Buerger³⁹ published the standard description in 1924. It may be added that Cornil and Ranvier,⁴⁰ in 1860, described "Oblitération des artères par endarteritis et thrombose," and pointed out that a coagulum may precede arteritis as well as arteritis precede a coagulum. Mention must be made of Rabinowitz,⁴¹ who recently claimed to have isolated a Gram-negative, rod-shaped, and beaded organism from a case of thrombo-angiitis obliterans, and to have produced by the bacillus the same lesion in the vessels of the ears and feet of rabbits as that which was present in the leg of the human. Parkes Weber's⁴² description of thrombo-angiitis obliterans as non-syphilitic arteritis obliterans of Hebrews no longer holds good. The disease attacks non-Jewish people. It belongs to the group of new diseases such as trench fever, hog cholera, and encephalitis lethargica.

In surveying the field we see that histology, in the work of Smee, Beale, Stricker, and Rouget, has made its precocious contributions. Gross anatomy and clinical surgery have opened a new line of advance determined by the investigation of the trophic lesions of cervical rib and their sympathetic origin. Leriche, Hunter, and Royle have given direction to the newer purposive surgery of the sympathetic system. Dale, Krogh, and Lewis are pioneers of a physiological and clinical line of attack. The protagonists of physico-chemical mechanisms are forging ahead. The whole of the experimental field, particularly as regards the comparative morphology of the sympathetic system, the comparative pharmacology, and the minute and laborious histology, calls for investigators. The histological work of the late Professor Kulchitsky at University College, London, was one of the mainsprings of the work of the late John Irvine Hunter. The recent surgical work in

America and Australia is promising. The Russian physiologists are extending our conception of the trophic nerves. The morbid anatomy of the blood vessels, as shown by the divers systems of classification of vascular disease in textbooks, is still chaotic. The clinical observations on the vascular diseases of the limb are limited to a few enthusiastic workers. Now, if ever, is the time to write in each hospital ward the following quotation: "Laboratory guides are mostly artificial, are reliable only in some instances, and are the handiwork of man; clinical symptoms are the natural, infallible, unalterable expressions of definite states, and are the ways of God." In each laboratory and dissecting room the text should be: "When the interest flags, strive to become the hero in the oldest of all tragedies—a deduction destroyed by a fact."

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INTRAVENOUS THERAPY.*

BY

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THIS method of treatment has a great many advocates—more, perhaps, on the Continent and in America than in this country—and a great many adverse critics. There are points for and against it, but I think it has now so far justified itself as to deserve a legitimate place in modern therapeutics. It seems better to put remedies intended to act on the blood stream itself, or on some distant organ only reached through the blood stream, directly into the veins, rather than into the stomach, where they must mix with the food and take their chance of being modified by the digestive juices, and finally be subject to the whim of the absorptive mechanism of the alimentary canal. On the other hand, remedies intended to act primarily upon the stomach or intestines are best put there through the mouth. The ease and apparent safety with which intravenous salvarsan injections can be administered has given a great impetus to the use of the intravenous route for purposes of treatment.

The following advantages have been claimed in favour of

the intravenous route: that the dose is more precise; that irritation of the gastro-intestinal tract is avoided; that the drug is not altered or destroyed in the alimentary tract; and that drugs act more promptly when given intravenously. I propose to criticize these in detail.

Precision of Dosage.—A medical man prescribes a remedy with the idea of producing a given effect; he desires to give the exact dose which will produce that effect—no more and no less. The appropriate amount is arrived at by giving repeated fractional doses by the mouth, each being well below the full therapeutic dose; it is assumed to be the dose required by the patient in the circumstances which obtain at that moment. The fractional dose can be increased until the desired effect is obtained. It is not practical to give repeated fractional intravenous doses of a drug; therefore the intravenous dose is more liable to err. For example, strophanthin acts powerfully when given intravenously, and a number of deaths from its use in this way have been recorded. It must be admitted that it is more difficult to arrive at the right therapeutic dose by the intravenous method than by giving a drug orally.

Absence of Gastro-Intestinal Irritation.—A drug which directly irritates the gastro-intestinal mucosa might be expected to irritate also the intima of the veins. The word "irritation" is used somewhat loosely in this respect; what is really meant is that the drug causes disturbance during the process of excretion. This applies more particularly to

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