

THE DEVELOPMENT OF THE HYOSPRAY FOR PARENTERAL THERAPY BY JET INJECTION *

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MECHANICAL inventions are frequently reproductions of natural phenomena. The looking glass is constructed to reflect an optical image, as does a clear spring of water. The airplane copies the dynamics of the bird in aviation. The rubber bulb syringe used by Auel in 1840 to irrigate the lacrimal duct duplicates the venom injection apparatus of the poisonous snake. The hollow needle constructed by Alexander Wood in 1853 resembles a mosquito proboscis.

However, the syringe and needle instruments for parenteral injection have not kept pace in development with other mechanical devices, since there has been no fundamental change in the basic principle of mechanical subcutaneous injection since 1853. During this decade a new idea for subcutaneous injection was developed by Lockhart, an engineer. He had observed injection through the skin of diesel oil under high pressure from fine jetlike leaks in conduits. Since many of these accidental injections were painless, he attempted to develop an instrument for medical injections. He was stimulated in his researches by his wife, who was a nurse. He produced an unwieldy instrument, inactivated by spring pressure, and obtained a basic patent. A well-known pharmaceutical company assisted him. Later, however, the R. P. Scherer Corporation, of Detroit, was called in as a collaborator in the early stages of the development. Because of mechanical problems, expenditure of large sums of money, engineering design and effort, only the Scherer Corporation continued the development of this new instrument long enough to make it effective. This instrument has been named the hyospray. It has been developed into a compact two-cell flashlight size instrument, constructed so that 125 pounds of spring pressure can be projected against a plunger, 0.5 cm. in diameter, into a bullet-size container of 0.25 cc. volume. In the blunt nose of the bullet is a microscopic orifice 0.003 inch, or approximately 76 microns, in diameter. This orifice is $1/136$ as large as that of a 20-gauge needle, and $1/37$ as large as a 26-gauge needle. According to Pascal's law, when this force of 125 pounds is projected against this small plunger

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within the metal container, a pressure is built up of approximately 3900 pounds per square inch. This projects a capillary-like column of liquid through the orifice of the metapule at a velocity of 600 miles per hour. Because of the minute size of the orifice, only 11 Gm. of pressure is developed by the jet. Frank H. J. Figge, Professor of Experimental Anatomy at the University of Maryland, has determined, by penetrometer studies on fresh cadaver and living human skin, that this is adequate to force the material through the skin, into the subcutaneous tissue and along fascia planes, along most dorsal surfaces and into the

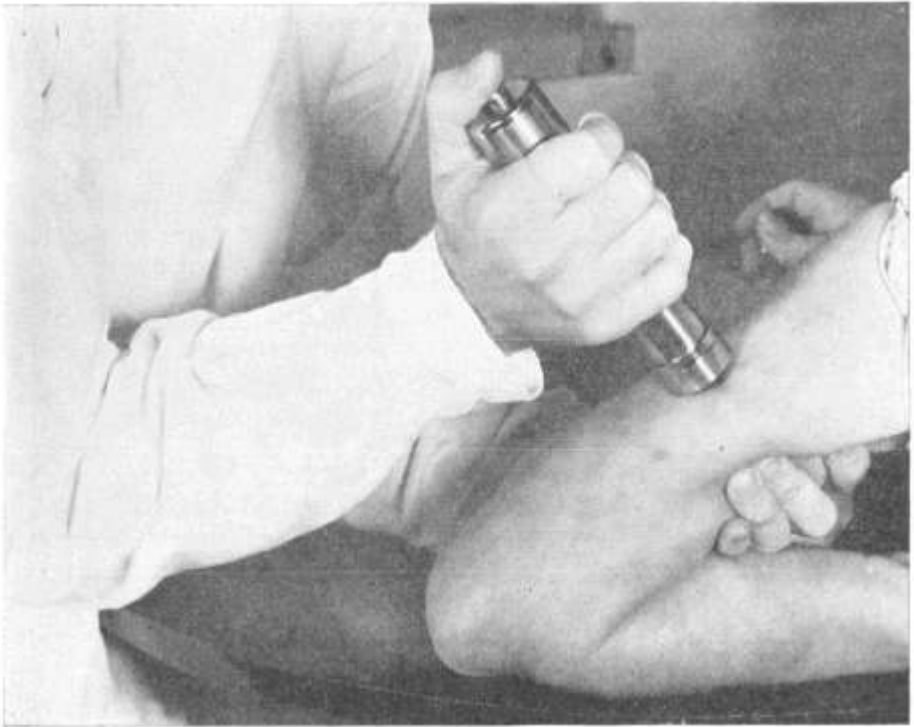


FIG. 1. Hypospray in position for the injection of promin into the tissues beneath a nodule of leprosy.

muscle planes on the volar surfaces. Indeed, it was Figge who worked tirelessly through many experiments with the engineers of the Scherer Corporation in developing optimum spring pressures and minimal effective orifices, which led ultimately to the hypospray in its present form.

Figure 1 shows the hypospray in position for the injection of promin into the tissues beneath a nodule of leprosy. Figure 2 demonstrates the internal spring mechanism. Figure 3 presents the fine spray-like dispersion of injected particles after the jet meets air resistance. Figure 4 presents the position of the hypospray on the lateral surface of the

forearm, with the pattern spread of 0.25 cc. of 30 per cent diodrast injected into the subcutaneous tissues. Figure 5 presents subcutaneous and intramuscular diodrast injections with different forces of spring pressure into the triceps region of the upper arm. Figure 6 shows the terminal phase of the hypospray pattern of spread against air resistance.

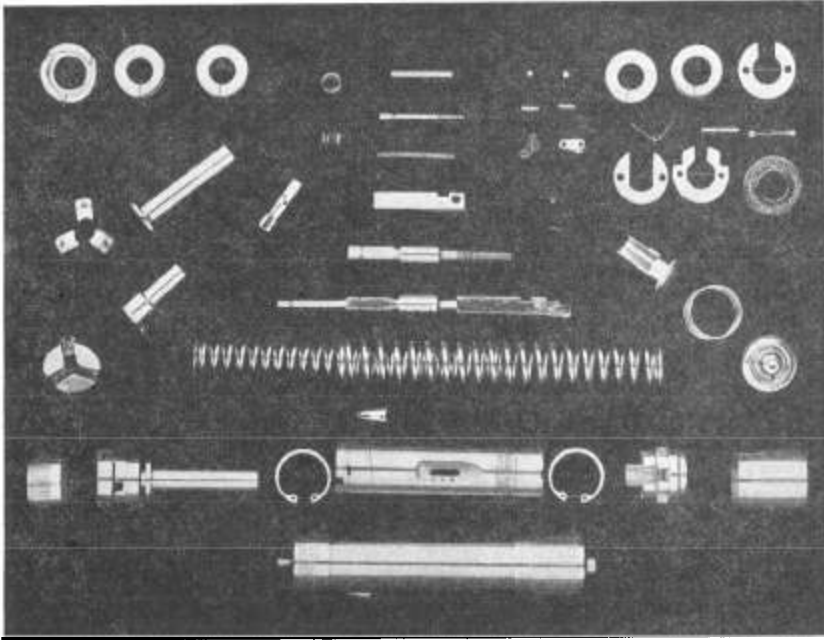


Fig. 2. Propulsion spring mechanism disassembled. (Courtesy of the R. P. Scherer Corporation, Detroit.)

In September 1947 Hingson and Hughes reported the first series of clinical studies with jet injection. At that time they had injected local anesthetics, diodrast, ephedrine, insulin, and penicillin, in therapy. They listed the following disadvantages: (1) the cost of the instrument and the metapules; (2) the present limited maximum dose of 0.25 cc.; (3) the necessity for developing different inert metallic containers for different active drugs; (4) the possible injury to tissue from high pressure jet injections; (5) the relatively wider dispersion of injected material as compared with the needle-syringe method. (This might prove to be a real disadvantage in the injection of toxoid, when slow absorption is desired. Fast absorption, on the other hand, might be a distinct advantage in the use of certain stimulant and analeptic drugs.) (6) The necessity of using less viscous solutions for certain medications, so that the solution will pass readily through the minute opening in the metapule; (7) the mechanical difficulties associated with maintaining this more technically complicated apparatus in operation.

Robert V. Brown, of the Division of Pharmacology of the University of Tennessee, set up a rigid group of experiments in which he attempted to investigate the possibility of intravenous injection with the hypospay. He found that if the jugular vein were located by anatomical dissection in the neck of a dog, an occasional hypospay injection

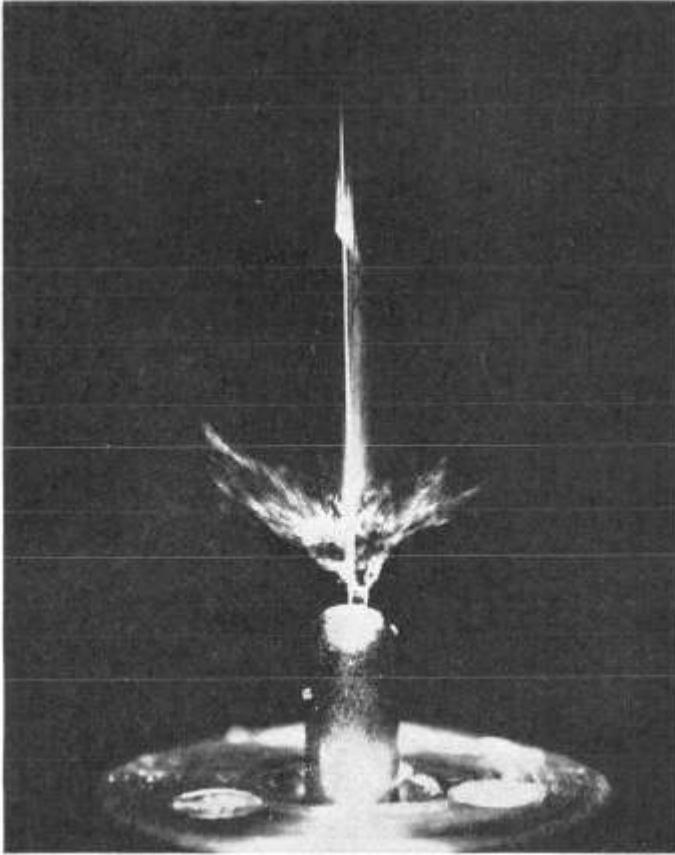


FIG. 3. The fine spray-like dispersion of particles of medicament after the jet meets air resistance.

could be made into the lumen of the vein when under direct vision the nozzle of the metapule was indented through the skin into a surgically secured empty and distended jugular vein. He concluded the following:

1. Under conditions most favorable for intravenous injection the jet injector has lodged as much as 98 per cent of the total available drug in the vein even when administered through skin and subcutaneous tissue.

2. Large veins are easier to "hit" than small vessels and retain a larger amount of the jet-injected material.

3. The probability of unintentionally penetrating a major vein with the jet is small but the risk is always present.

4. Absorption of jet-injected material from muscle or subcutaneous tissues appears to be more rapid than that of needle-injected material.

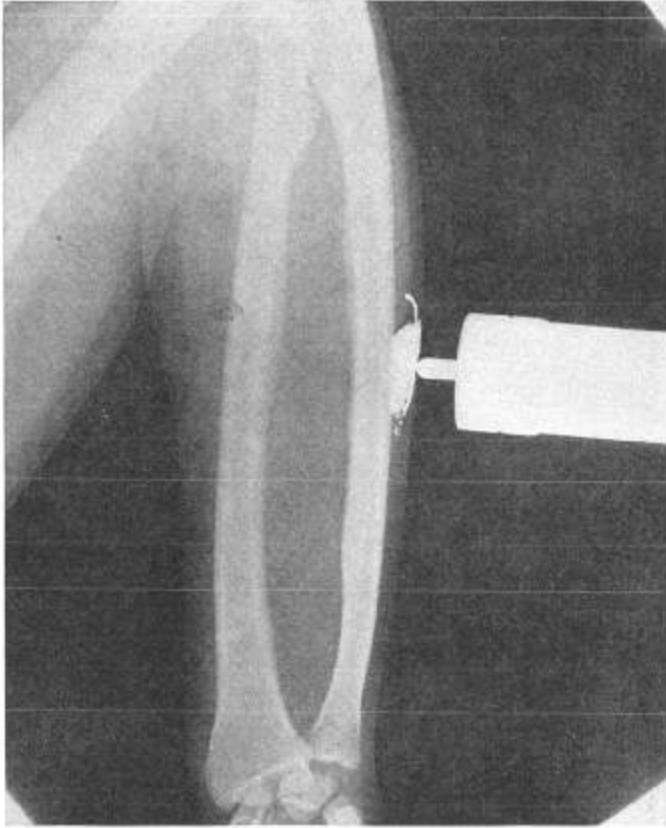


FIG. 4. X-ray study of the hypospray on the lateral surface of the forearm with the pattern of spread of .25 cubic centimeter of 30 per cent of diodrast injected into the subcutaneous tissues. (Courtesy of Dr. Frank H. J. Figge, Anatomy Department, University of Maryland.)

On the basis of this work he made certain general recommendations :

1. Jet discharges should not be made in the neighborhood of large blood vessels unless the drug to be injected is safe both in concentration and pharmacologically for intravenous administration.

2. Upon general release of the instrument, physicians should instruct patients on presumably safe sites for injections before prescribing any self-medication.

3. Certain drugs should never be loaded in cartridges except for experimental work.

4. Certain drugs might well be loaded in several concentrations: some reasonably safe for home use, some for sale on prescription only.

This substantiated the previous recommendations of Figge. We are in concurrence with these precautions, but, on the basis of clinical experience with jet injection now of more than 5,000 patients, we do not believe that the possibility of inadvertent intravenous injection is as

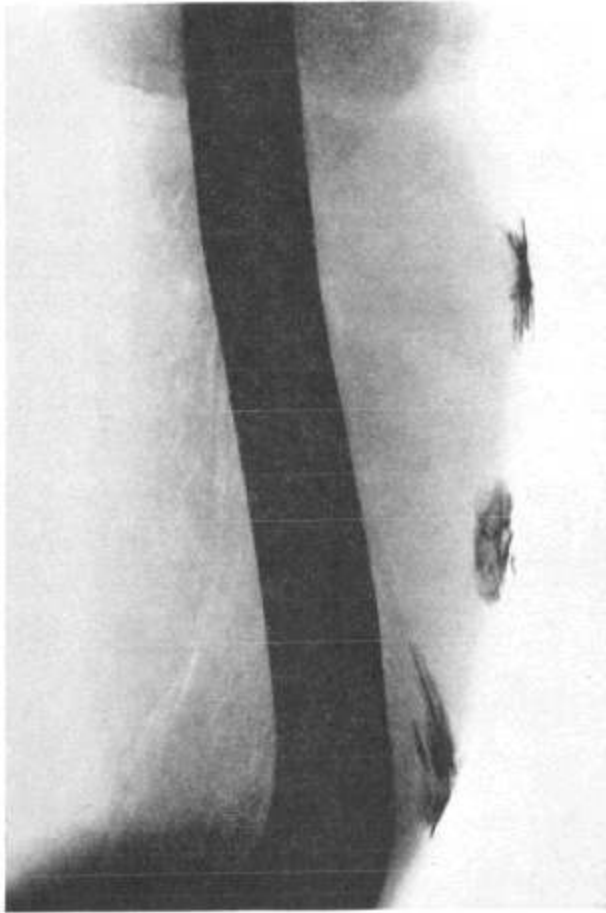


FIG. 5. Subcutaneous and intramuscular diodrast injections with different forces of spring pressure into the triceps region of the upper arm. (Courtesy of Dr. Frank H. J. Figge, Anatomy Department, University of Maryland.)

likely as with the needle and syringe method. Furthermore, since the diameter of the jet is only $1/37$ that of a 26-gauge needle, we are convinced, by both clinical and histologic study of tissue, that there is less trauma with the hyospray than with the needle and syringe.

Consequently, we strongly emphasize the advantages of hyospray injection over that of the needle and syringe technic. The advantages

are the following: (1) The complete absence of pain in half the subjects so injected, and the diminution in pain in the majority of the other individuals injected. (2) The mechanical protection and preparation of the metapules, so that sterilization of the instrument before use is unnecessary. (3) The tested fact that children about to be injected do not



FIG. 6. The terminal phase of the hypospray pattern of spread against air resistance.

fear the instrument so much as the syringe and needle when they are approached for a first injection. Their actual experience with one injection convinces them that subsequent injections will be painless or nearly so. (4) In the field of pediatrics and in military immunizations, the use of this instrument would save time of multiple sterilizations of equipment. (5) For the administration of drugs by daily injection over long periods, such as insulin and penicillin, this seems to be the

instrument of choice. (6) In the field of therapeutic nerve block for relief of pain in a wide variety of conditions this instrument and method holds great promise.

In order to determine the comparative effectiveness of the therapeutic injection of penicillin in the treatment of gonorrhoea with the hypospray as compared with a simultaneous control study with the

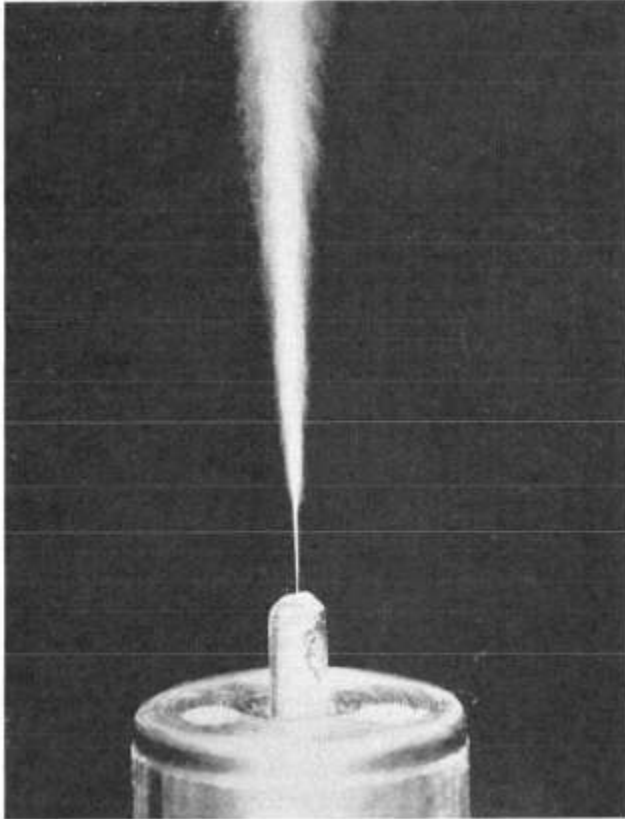


Fig. 7. Hypospray jet and spray magnified ten times.

needle, we undertook an evaluation study at the Rapid Treatment Centers in Memphis, Tennessee, Meridian, Mississippi, and Hot Springs, Arkansas. The following criteria were established for the study:

1. In all selected patients, the diagnosis of gonorrhoea was based on a positive culture confirmed by sugar-fermentation tests.
2. All patients were hospitalized for a period of ten days following treatment.
3. To be considered cured, the patient had to be bacteriologically free from infection, as indicated by four negative cultures during the ten-day observation period after treatment. Cultures after treatment were usually performed on the second, fourth, sixth, and tenth days.

4. Every fourth male and every fourth female were given treatment by needle injection.

A total of 206 patients fulfilled the requirements for inclusion in the study, of whom 158 were given penicillin by hypospray and 48 by needle administration. Of the 206 patients, 93 per cent were Negro and 7 per cent were white; 76 per cent were males and 24 per cent were females.

Table 1 shows a cure rate of 97.9 per cent among patients given the penicillin schedule by needle injection. The cure rate in this series is approximately 4 per cent higher than the 94 per cent cure rate obtained with the same treatment schedule, utilizing 2 morphous penicillin, administered to a series of 255 patients with gonorrhoea eighteen months ago (3). The results obtained with the administration of penicillin by hypospray were almost identical with those obtained by needle administration (97.5 per cent cure by hypospray as compared with 97.9 per cent by needle).

Thus, this study shows, in the first therapeutic evaluation of the instrument, that penicillin in water solution administered by hypospray is as effective as that administered by syringe and needle. It is much less painful. There is less personnel required for sterilization. A disadvantage at the present time, however, is that water-soluble penicillin deteriorates in from three to seven days under refrigeration. Penicillin crystals in oil, to become effective in maintaining prolonged blood levels, should be on an average of 40 to 50 microns in diameter. It can readily be seen that the penicillin in oil with crystals of this size could not be effectively discharged through a 75-micron orifice, because several of these crystals at the high velocity of 600 miles per hour would obstruct the orifice. At the present time we are investigating the use of procaine penicillin in smaller particle sizes for this purpose.

For the Relief of Pain.—During the past year the hypospray has been used on several thousand patients without serious complications; those complications encountered were of no more severity than the traumas associated with the insertion of 26-gauge needles. By using 6 per cent procaine in 0.25 cc. metapules pain has been relieved instantaneously and for prolonged periods in the following conditions: (1) acute bursitis (especially around the deltoid insertion). (2) The neuritis of leprosy. In some of these patients relief of excruciating nerve pain begins within a few minutes after injection and lasts for several days. (3) In acute muscle and ligamentous strain. (4) Intercostal neuralgia. (5) In painful neuritis and arthritis about the wrist, ankles, hands and feet. (6) In angiospastic diseases of the upper extremity hypospray injection into the region of the ulnar nerve at the elbow relaxes the sympatheticomimetic constriction. (7) Brody and Quigley reported successful relief of cardiac pain when 2 per cent and 4 per cent procaine through the 0.25 cc. metapule is injected over the precordium into the region of greatest discomfort.

During the past few months the principle of the hypospray has been extended from the 0.25 cc. to the 1 cc. instrument. Experimental work is now being carried out determining the technic and safeguards necessary for the use of this larger injector. It is possible to measure accurately the amount of medicament to be injected with this improved instrument in units of 0.001 cc. to 1 cc.

Hughes at the present time is evaluating the use of various spring-strength hyposprays for different size children in pediatrics. He has determined that blood levels of streptomycin and penicillin are as high when the agents are given by jet injection as when they are given by needle technic. This work on children confirms the previous work of Hirsch of the Pure Food and Drug Division, who determined blood levels of penicillin and streptomycin with the hypospray on adults.

The hypospray presents a new approach to all types of parenteral injection. The advantages and disadvantages have been emphasized.

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