INTRAVENOUS PROTEIN THERAPY.*

BY

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By "intravenous protein therapy" is implied the intravenous injection of a "foreign" protein in the treatment of disease. A "foreign" protein is one not normally present in the tissues of man. Intravenous injection of certain proteins in certain doses gives rise to a chain of symptoms and signs to which the expressive but misleading term "protein shock" has been applied by American workers.

Various proteins have been employed, mainly in the form of bacterial emulsions, though peptone is of value in several conditions. Of bacterial emulsions, the protein complex of the coli-typhoid group of micro-organisms is more efficacious in inducing this "shock" reaction than is that of other species; and when such a reaction is desired, it is a vaccine of typhoid or colon bacilli that is most frequently employed, and the remarks immediately following apply solely to the reaction induced by that type of antigen which may be given either plain or sensitized.

Dosage.

Within fairly wide limits the size of the dose has but little effect on the severity of the reaction. Thus a higher temperature response has been experienced after an initial dose of 50 million killed *B. coli* vaccine in one patient than after 200 million of the same vaccine in another, though it must be admitted the general constitutional disturbance was greater in the latter. The initial dose for an average adult may with perfect safety lie between 50 and 100 million, though Gay,¹ in the treatment of typhoid fever, advocates 150 million sensitized typhoid vaccine as a first dose. Cecil² mentions that by an error in technique 400 or 500 million killed typhoid bacilli were given as a first dose to three of his patients with arthritis, yet the reaction was little, if any, more severe than that caused by smaller doses, and the therapeutic effect was no better.

In order to effect the desired result it is necessary to produce a moderate reaction. The dosage in successive injections must be progressively slightly increased so that a like train of symptoms may follow each inoculation.

Technique of the Injection.

The patient is confined to bed for twenty-four hours at least. In order to lessen as far as possible the nausea and liability to vomiting commonly met with, especially after a first injection, a mild aperient is given the evening before. A light breakfast is advisable, and the injection should be made, if possible, before midday, so that the transitory unpleasantness of the reaction may be over before night.

The requirements are: (1) Ether and wool to clean the skin. (2) A sterilized needle and syringe of 10 c.cm. capacity. (3) The vaccine containing, say, 100 million coli or typhoid bacilli per cubic centimetre. (4) Ten c.cm. of sterile warm normal saline solution. This is for diluting the vaccine, as it is more convenient if the volume of the injection measures 10 c.cm. rather than $\frac{1}{2}$ or 1 c.cm., as the larger quantity is easier to handle, and the dose of protein can be given more slowly. (5) Adrenalin solution 1 in 1,000, or $\frac{1}{100}$ grain tabloids of atropin sulphate. (6) An assistant to help in filling the syringe and to constrict the patient's arm, and thus render prominent the veins in the antecubital fossa, is also desirable. Dr. R. G. Canti has designed a very simple tourniquet, easy to release, which is admirably suited for the latter purpose.

Method.—The skin over the selected vein is cleansed, and the desired dose of vaccine, whether $\frac{1}{2}$, $\frac{1}{4}$, or 1 c.cm., is drawn into the syringe, and the volume made up to 10 c.cm. with normal saline. The assistant now applies the tourniquet, or constricts the upper arm, which is lying flat on the bed fully extended, and the patient is told to open and clench the fist several times until the vein on the front of the elbow becomes prominent; in some individuals the veins are more easily felt than seen. The needle of the syringe is inserted into the vein in the usual manner of vein puncture; a successful puncture is indicated by a flow of blood into the syringe. The assistant now relaxes the tourniquet (or his hold on the arm), and the injection is made very slowly; that the fluid is entering the vein and not the perivascular tissues is shown by complete absence of swelling in the region of the needle point. When the contents of the

syringe have been pushed into the vein the needle is withdrawn and the arm held vertically upwards for a few minutes to prevent extravasation of blood; no dressing is required.

The Reaction.

General.—In the afebrile human subject the intravenous injection of from 50 to 100 million killed coli vaccine is followed by a very definite train of symptoms which comprise the so-called "protein shock reaction." For a period varying from three-quarters of an hour to five hours the patient will experience no abnormal sensations, but after that symptoms will appear somewhat suddenly. The earliest symptom is commonly an involuntary twitching of the muscles of the legs. This may spread to the trunk and become general without the patient at first feeling cold, and last, perhaps intermittently, for from fifteen to forty-five minutes; the onset of the rigor is occasionally preceded by a dull ache in the back or shins.

Before the shivering is finished the patient commonly has abdominal discomfort with nausea and, not infrequently, vomiting; he has headache, which is usually frontal and sometimes pronounced. In a reaction of unusual severity the patient may be restless with dyspnoea and cyanosis. Such symptoms are speedily relieved by a hypodermic injection of 0.75 c.cm. of 1 in 1,000 adrenalin or $\frac{1}{100}$ grain atropin sulphate.

As the reaction passes off, especially if it be after a second or third injection, general pains in the limbs, with cutaneous hyperaesthesia, may be complained of for a short time; yawning is frequently seen. As a rule the patient is quite free from headache and other discomfort after the seventh hour, though exceptionally facial herpes may develop two or three days later, with or without tender areas in the skin.

Just prior to the onset of the shivering the temperature begins to rise, and continues to do so until about the sixth hour. It commonly reaches 103° or 104° before returning to normal at the end of twenty-four hours; defervescence may be interrupted by a short secondary rise of a degree or so. With succeeding injections of increased dose the fever, though reaching an equal height, is apt to be of shorter duration, and the whole reaction is more quickly completed.

The pulse frequency also is increased during the reaction, and extra-systoles may occur during the rigor, and for a short time afterwards. The increase of the pulse frequency is generally of somewhat longer duration than is the raised temperature.

*Blood Pressure Changes.*³—The systolic blood pressure usually shows a fall of a few millimetres before any symptoms are evident. During the rigor I have met with a small rise on two occasions only, and that either to the preinjection figure or a few millimetres above it; more generally the fall continues for twelve hours or so, the reading then being about 20 mm. below the initial figure. The systolic blood pressure is commonly normal again after twenty-four hours. The diastolic pressure generally rises appreciably within the first half-hour. The rise may continue until the end of the rigor, but more frequently this pressure drops rapidly after the first half-hour, and may be at its lowest by the end of the second hour—perhaps a drop of 30 mm. in an hour and a half. It tends to remain at this level for twelve hours or so, but is normal again in twenty-four hours.

*Cytological Changes in the Blood.*³—The intravenous injection of *B. coli* vaccine causes an almost immediate fall in the white blood cells. Following a first injection the retreat of the polymorphonuclears from the peripheral circulation is hurried, and by the end of the first hour they may be outnumbered by the lymphocytes. A rapid increase follows the rigor, and the maximum of 20,000 to 30,000 per cubic millimetre is reached in twenty-four hours; during the leucocytosis neutrophil myelocytes frequently appear, and normoblasts have also been met with. The rise in the number of the circulating leucocytes is succeeded by a steady fall, the preinjection figure being reached in approximately seventy-two hours. Though the fall in the lymphocytes is less abrupt, it is a very striking feature of the blood picture, and of far longer duration than is the polynuclear leucopenia. It is not followed, however, by a lymphocytosis.

The intravenous injection of *peptone* must be made very slowly, or somewhat alarming symptoms may arise rapidly. When giving *peptone* as a 10 per cent. solution I use a very fine needle, a No. 28 or 30, and, as recommended by Nolf,⁴ a nurse keeps constant observation on the pulse frequency, calling out the number of beats in each quarter of a

* An abstract of a paper read before the Hunterian Society on January 28th, 1920.

minute. If this exceeds 35 per quarter the injection is temporarily stopped.

On one occasion when giving the fourth of a series of peptone injections to a patient with streptococcus infective endocarditis, when 10 c.cm. had been given the pulse frequency suddenly increased. In successive quarter minutes the figures were 26, 26, 28, 34—injection stopped—38, 43, 36, 34, 34, 28, 26—injection restarted—28, 26, 26, and, shortly after, 22. The patient, not highly intelligent, said that during this time he felt giddy and "as though his head were going to blow open." He experienced a tickling in the throat, a stomach-ache, and he began to cough, the face became suffused and he sweated a little. The subjective disturbance lasted not more than three minutes.

These symptoms accompany, and are doubtless the outward and visible sign of, a considerable drop in blood pressure and a very rapid fall in the circulating leucocytes induced by the peptone, or primary proteose present with it in solution.

Just as the populace fled from the streets for cover in the tubes on the warning of an air raid, so on the approach of peptone do the leucocytes decamp from the peripheral circulation for the shelter of the pulmonary capillaries, and it is not until an "all clear" is sounded that they emerge from their retreat, accompanied by others, to mark the result of the invasion. With certain doses of peptone these changes take place with extreme rapidity—so much so that it is difficult to obtain accurate records of them—in a moment, in the twinkling of an eye, they are passed. And it is very surprising that in most instances they are unaccompanied by any symptoms whatever appreciable to the patient, who remains in all respects oblivious to the ferment within him. The injection of peptone may likewise be followed by a rigor an hour or so later, but I have never found peptonuria.

It is obvious from the foregoing description of the clinical symptoms and signs that are wont to follow upon the intravenous injection of certain proteins in certain doses that the reaction is in no sense a "shock" in the usually accepted surgical application of the term. Following immediately on a surgical operation, if the patient survive, three phases are commonly seen, termed respectively, "Shock," "Reaction," and "Traumatic Fever." The stage of "Shock" is characterized in the main by subnormal temperature, high pulse frequency, and lowered blood pressure. This is succeeded by "Reaction," in which there is a return of the temperature to normal and a fall in the pulse frequency. Nor does the reaction come under the heading of the so-called "Anaphylactic Shock," which is brought about in the animal body by the reinjection of a foreign protein after the lapse of a certain period of time. Following the initial or sensitizing injection the animal may become "hypersensitive" to the specific protein, so that it reacts in a peculiar fashion to a second or intoxicating dose. Such a reaction may on occasion resemble that of "protein shock" in certain important features, but it differs from it in other essentials. To avoid confusion Auld⁴ has suggested "pyrogenic" as a distinguishing term for the reaction under consideration, but this also is not without objection. Fever may follow the intravenous injection of a number of substances containing no protein, and further, the clinical improvement consequent on the injection cannot be ascribed to the short bout of fever produced thereby. A cumbersome but expressive and non-committal title would be the "Intravenous Protein Reaction," and its practical application, "Intravenous Protein Therapy."

Types of Cases Benefited.

The diseases in which benefit by this form of treatment has been reported fall into four main groups:

1. Infective disease in which the causal organism is known and in which the vaccine is given intravenously both for its specific and possible "shock" effect; for example, typhoid fever, coliform infections of the urinary tract, and the septicaemias.
2. Infective disease in which the causal organism is unknown or not certainly determined. Here the protein is given solely as a non-specific factor in the treatment of the affection. This group includes rheumatic fever and multiple infective and rheumatoid arthritis.
3. Infective disease in which the causal organism is known but in which specific vaccine therapy is of little value. Here also a protein is given entirely for its shock effect; for example, pneumonia, gonorrhoeal arthritis.
4. Chronic disorders of doubtful or unknown etiology: psoriasis, pemphigus, lupus erythematosus, bronchial asthma.

In *typhoid fever* both sensitized and unsensitized typhoid vaccine has been used by several workers; Gay¹ summarizes their results, and adds 98 cases of his own, which show a mortality of 6.6 per cent. and 13 complications.

Gay states that the milder cases of the disease react better to the treatment than the more severe, but even the most severe will, in some instances at least, be benefited and even aborted. The usual dose of the initial injection was 150 million, and the dosage in successive inoculations was slightly increased in order to produce a similar reaction. He states that in typhoid fever the injection is followed in from fifteen minutes to an hour by a chill, which may last for a quarter of an hour, and is accompanied by a rise in temperature of one to three degrees, reaching its maximum within three hours and then falling, reaching normal or subnormal in about twelve hours, with sweating and usually improvement of such symptoms as headache, delirium, etc. If the temperature again rises over a period of two or three days, a slightly increased dose is given; if no striking result follows three or four injections at two or three days' interval, very little improvement from further treatment on the same lines is to be expected. The disease in one-third of the cases in his series was aborted, benefited in another third, while in the remainder it was unaffected; the liability to complications appeared to be diminished, but as a means of preventing relapses the injections are of little value.

Nolf² speaks highly of the value of peptone in the treatment of the typhoid fevers. He found morning injections more efficacious than those made in the afternoon, possibly because the patient was fasting, and acting on this hypothesis he is accustomed to allow his subjects nothing but water from the night before.

The reaction induced by peptone is proportional to the dose; in an adult 5 to 6 c.cm. of a 10 per cent. solution produce a rise in temperature in one to two hours lasting for several hours; 7 to 10 c.cm. have the same immediate effect, but possibly in addition a rigor followed by sweating and a rapid fall of temperature to normal. Other things being equal it seems that a complete reaction—that is, one accompanied by a marked and persistent fall in temperature—is more difficult to produce in the first ten days of typhoid than later.

Thus it would seem that in the early stages of the disease the best effects may be expected from sensitized vaccine and in the later from peptone; perhaps peptone and vaccine should be given together after the second week of the fever.

I have employed an autogenous coli vaccine intravenously in the treatment of *pyelonephritis* with good result on several occasions. One case of two months' duration in a man showed a tender swelling in the right renal region, pyrexia, and 10 per cent. of pus in the urine. After four injections the urine became free from cells and bacilli and was still sterile when last examined six months later.

A female, aged 38, was admitted to the medical clinic of St. Bartholomew's under Sir Archibald Garrod, with the history of a sudden onset of pain during, and frequency of, micturition five weeks previously, associated with haematuria and a temperature stated to have been 105°. Her right kidney was palpable and a little tender; she had red blood cells and an abundance of pus and coliform bacilli in the urine. As her condition did not clear up on alkalis and urinary antiseptics, she was given an autogenous plain vaccine intravenously. The first dose of 100 million gave rise to no abnormal sensations for five hours, but then mild shivering began, which lasted an hour, associated with slight headache and nausea; there was no abdominal pain, but some increase in frequency on micturition during the night—she was not quite comfortable again for forty-eight hours.

This reaction is mentioned in some detail as it shows that when an autogenous coliform vaccine is employed the onset of the reaction is apt to be considerably delayed in point of time. Two further injections were given to this patient at seven and five days' interval, and she was discharged free from pyuria and bacilluria.

In *pyogenic infections*, both local and general, vaccine may be administered by the intravenous route. In cases of septicaemia, using a plain or sensitized vaccine alone, it is difficult to produce a rigor; I am convinced on clinical grounds that the ultimate results are better, in really desperate streptococcal cases, when such a reaction occurs. As to the nature of a rigor I am in ignorance, but one is more likely to ensue if, in addition to the sensitized vaccine intravenously, anti-streptococcus pyogenes serum is given subcutaneously at the same time, possibly owing to the more rapid liberation of endotoxin. The improvement of the patient on such treatment may not be entirely recorded on the chart, for the general condition is bettered before the temperature falls—the dusky look is lost, the tongue moistens, the patient sleeps

and eats much better than before; indeed, in those cases which are going to respond a striking improvement in the general condition takes place in a couple of hours or so.

Local streptococcal infections are also often abated by intravenous vaccine.

A patient who had miscarried at the sixth week was admitted five days later to hospital, under Mr. Rawling, with a rapidly spreading cellulitis of both arms and the right calf and severe constitutional disturbance. Blood culture was negative. Twenty-four hours after an intravenous injection of 500×10^6 sensitized streptococcus vaccine her general condition was much improved; she had lost her pain and the redness and swelling had greatly diminished. A second dose, of 1,000 million, was given, and the inflammation in the left arm entirely disappeared, and in the right arm and leg it became localized with pus formation, which subsequently required draining.

In the febrile subject it is exceptional for the intravenous injection of streptococcus vaccine to produce a sharp rise in temperature, but in the afebrile a brisk thermal reaction may result.

A traumatic ulcer of the foot, consequent on a wound sustained in the Zeebrugge raid, which resisted subcutaneous vaccine and antiseptic treatment for five and a half months, healed rapidly after one intravenous injection of autogenous sensitized streptococcus vaccine. The dose of 100×10^6 produced a sharp reaction—shivering at the nineteenth hour and a rise of temperature which lasted for eighty hours, reaching its maximum of 104.2° at the twentieth hour.

I have given peptone intravenously in conjunction with sensitized vaccine subcutaneously in streptococcal septicaemia, and am convinced of its value in such cases. Nolf⁷ maintains that intravenous injections of peptone not only check the course of streptococcal and staphylococcal septicaemias, but are also useful in severe local infections as a stimulant to the forces of defence.

In certain forms of arthritis great benefit may be derived from intravenous protein therapy. Here the vaccine is given entirely for a shock effect. The type of joint disease which responds best, in my experience, is the multiple infective arthritis for which no active source of primary infection or septic absorption is demonstrable. The patients are free from pyorrhoea, tonsillitis, sinusitis, chronic skin or urogenital infections, and present no other suggestion of intestinal toxæmia.

The disease syndrome comprises muscular wasting around, pain in, and deformity of, both smaller and larger joints, the main lesion being in the soft periarticular tissues rather than in the bones or cartilage, and osteophyte formation with erosion of cartilage characteristic of senile osteo-arthritis is not seen. These changes are prone to begin symmetrically in the proximal interphalangeal or other small distal joints before the larger articulations are involved. A low fever, increased pulse frequency, and slight enlargement of superficial lymphatic glands may accompany the joint changes. Albuminuria is a late development.

In such cases, provided treatment is instituted sufficiently early, I believe one is justified in saying that there is a good chance that the course of the disease may be arrested and the pain and fever abolished. In a certain proportion the periarticular swelling will be considerably reduced and the range of movement correspondingly increased, but it is obvious that when marked structural alteration has already occurred, leading to subluxation, deflection, etc., one cannot hope for complete anatomical restoration. The following are examples of those so treated by me:

A. P., male, aged 13, under the care of Dr. James Calvert. Eight months' duration; steadily progressive, involving both hands, wrists, ankles and knees, and the cervical spine. Was just able to walk with the aid of two sticks. Much pain. Evening temperature rarely above 100° , though occasionally 101° F. No albuminuria. After the fourth injection the note says, "he has lost pain in and stiffness of joints, and has abandoned his sticks when walking. Left knee can be straightened completely and the right nearly. Neck is improved. Both wrists less swollen, especially the left. Interphalangeal joints still much swollen, but swelling quite gone from ankles and very nearly from knees. No fever." Eleven injections were given altogether. He is now well, able to play football and the violin.

A. A., female, aged 29. (Dr. Morley Fletcher.) Twelve months' duration. Both hands, knees, elbows and shoulders. No albuminuria. Low irregular fever, not above 100° F. Much pain, especially at night. Given seven injections; the first of 100×10^6 T.A.B. was followed by a temperature of 104.2° F. and herpes of the lower lip. Fever and pain quickly stopped,

swelling slowly disappeared, and she was able to sew and walk without pain or difficulty on her discharge.

E. J., female, aged 40. (Sir Archibald Garrod.) Seven years' duration. Both wrists, metacarpal and inter-phalangeal joints and both knees. No fever. Four injections given. Joints stiff in morning, but not painful; much less periarticular swelling, and is able to sew. Middle finger of left hand, which was flexed, is now straight.

The next is a case in which an immediate improvement was not maintained.

Mrs. N., aged 60. Six years' duration. All joints of extremities involved. Walked with difficulty; unable to dress herself; much pain. Trace of albumin in urine. She was considerably improved for a couple of months, being quite free from pain and able to walk and dress herself without difficulty. But the latest report says the pain and swelling in the knees has returned.

In the following case the pain was relieved and the fever abated, but there was no obvious change in the swelling or deformity, and the patient remained bedridden.

A. B., female, aged 22. (Dr. Morley Fletcher.) Fourteen months' duration. All joints of extremities involved, with much flexion of knees and elbows. Low irregular fever and albuminuria. Twelve injections of T.A.B.; also given rheumatism "phylacogen" both subcutaneously and intravenously.

These cases may be supplemented by a brief summary of some of the records published by others.

Cecil² reports on 40 cases of rheumatic fever, acute toxic arthritis, and gonorrhoeal arthritis treated by intravenous injection of typhoid vaccine. In rheumatic fever and "non-specific" arthritis about 40 per cent. are stated to have recovered completely in two to ten days without salicylate, and most of the others were much improved. In rheumatic fever the average number of injections required was two, the dose varying from 30 to 100 million; salicylate was given if one or two doses of vaccine proved incapable of producing recovery. His seven patients with gonorrhoeal arthritis were benefited but little if at all. In one case of chronic gonorrhoeal arthritis and fibrositis marked improvement in the pain and stiffness followed the intravenous injection of a diphtheroid bacillus which I isolated from the urine after prostatic massage.

Peterson³ records a case of "acute multiple arthritis" which received at intervals doses of typhoid vaccine intravenously on three occasions and was thereby much improved. The precise nature of the arthritis is not revealed.

Miller and Lusk⁴ also report favourable results in the treatment of acute and chronic arthritis by the injection of foreign protein.

Nolf⁵ considers that the addition of peptone intravenously to salicylate treatment renders the latter more efficacious in certain obstinate cases of articular rheumatism, and that peptone in association with salicylate enlarges the group of acute arthritides amenable to salicylate treatment.

Certain other acute infections have been treated, in some instances with success, by the intravenous injection of typhoid vaccine.

Squier¹⁰ mentions two cases of influenzal pneumonia in which two transfusions with immune blood caused no reaction or change in the patients' temperature, pulse, respiration rate, or general condition, yet the injection of typhoid vaccine was followed immediately by a dramatic improvement.

Cowie and Beyan,¹¹ using typhoid vaccine in influenzal pneumonia, obtained no improvement in cases injected after the third day of the pneumonia, while all recovered who were so treated before the third day.

The skin lesions of psoriasis and lupus erythematosus may be relieved temporarily by injections of coli-typhoid vaccine. The condition apparently always relapses during the course of a few weeks or months.

Auld¹² has reported good results in the treatment of bronchial asthma by the intravenous injection of small doses of peptone. He states:

The cases best suited are those characterized by favourable intervals, with freedom from bronchitis and much attendant emphysema. The more recent the disease and the more regularly spaced the intervals the better the result. . . . Peptone stops the attacks over a period roughly proportionate to their former frequency. Generally speaking, the initial dose is 0.3 c.cm. of a 2 per cent. solution of Witte's peptone, increased by 0.2 c.cm. every fifth day until six injections have been given. Three or four more injections are to be given, employing in each the same dose as that given in the sixth injection. No reaction appreciable to the patient occurs. No injection is to be given during attacks, and when the latter occur at long intervals begin the treatment about three weeks before one is expected.

While I believe intravenous protein therapy to be of great value in certain carefully selected cases—more particularly of arthritis, the septicaemias, and coliform infections—I do most emphatically say that it is not a panacea for all ills; and even in those diseases in which it is of

use it is to be regarded solely as an accessory weapon in our armament for employment in conjunction with, not to the displacement of, other remedies.

I wish to express my thanks to those members of the staff of St. Bartholomew's who have allowed me to refer to patients who have been in their charge.

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THE POISON OF THE SPINY DOG-FISH.

A CASE OF ACUTE OEDEMA THE RESULT OF A PRICK BY A DOG-FISH, AND A PRELIMINARY NOTE ON THE POISON GLAND OF THE SPINY DOG-FISH.

BY

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TOWARDS the end of October, 1919, a fisherman came up to the Lowestoft Hospital complaining of a poisoned hand. There was a punctured wound at the base of the thumb

FIG. 1.—Section of gland showing ducts and vacuoles. A, Duct cut obliquely. B, Duct cut transversely. C, Vacuoles. D, Vacuoles bursting into inner end of duct. E, Duct. (From a micro-photograph by Dr. D. Hutchinson of a section by the author.)

Six hours previously he had been pricked by a dog-fish. The injury was followed by acute stabbing pain in the part which lasted four or five hours; the hand then began to swell, and when he arrived at the hospital there was great swelling and oedema of the back of the hand, and the front of the wrist and forearm were painful, tender, red, and oedematous.

This acute inflammatory oedema lasted for four days and for a time it seemed that suppuration would occur. On the fifth day the oedema at the back of the hand had subsided, but it was not until seven days had elapsed that the tenderness and swelling over the wrist had disappeared and the patient was convalescent.

The treatment adopted was to paint the hand and the front of the wrist and forearm with liniment and solution of iodine in equal parts and to apply hot fomentations.

Owing to the length of time that had elapsed since the injury no special treatment was applied to the wound; if the case had been seen earlier a weak solution of potassium permanganate would have been injected into the site of the puncture, as this is known to have an immediate effect on the pain and symptoms of poisoning in cases of the sting from the envenomed spines of the greater and lesser weever.

As this was the first case of injury by a dog-fish that had occurred in my experience, I was anxious to investigate

the nature of the poison if any existed, and for this purpose I obtained a number of fresh spines, which at that time could be easily obtained from the steam trawlers which were landing large catches of dog-fish.

The Spines and Poison Gland of the Spiny Dog-fish or Spur-dog, Acanthias vulgaris (Gray, Cat. British Museum).

This, the commonest dog-fish, also known as the picked dog-fish, under which name it is described and pictured by Couch,² has a sharp, strong spine in front of each of the two dorsal fins. The usual length of the fish is from 18 in. to 2 ft.

Spiny dog-fish. After Cunningham.

The accompanying sketch is taken from Cunningham's *Marketable Marine Fishes*,¹ and shows diagrammatically the position of the two dorsal spines.

The anterior spine is the longer, is slightly curved, and measures an inch or more in length, while the posterior is nearly straight, and is shorter—from half an inch to three-eighths of an inch in length. The posterior aspect of each spine is grooved, the groove becoming more shallow towards the point.

When examined with the naked eye, each groove is seen

FIG. 2.—Section of gland showing basement membrane and columnar cells. A, Vacuoles. B, Commencing formation of vacuoles. C, Columnar cells. D, Basement membrane. (From a photograph by Dr. D. Hutchinson of a section by the author.)

to be occupied by a glistening, pearly-white substance, and towards the base there may be seen in its centre a small linear depression about one-sixteenth of an inch long, which is often discoloured, possibly by the presence of a secretion poured out by the glandular structure in the centre of which it lies.

This pearly-white structure was removed from the groove and teased on a slide; the teased gland showed follicles in which layers of epithelial cells could be demonstrated surrounding a central mass of cells and granular matter staining by the van Gieson method, just as does the secretion of the weever's poison gland. Small detached portions showed columnar cells against a basement membrane, and upon them layers upon layers of round and cubical cells, some vacuolated, and some distended with granular matter in which the nuclei alone were distinguishable.

I have cut a series of sections of the hardened gland, the details of which I hope to publish elsewhere. The gland consists of a number of follicles which discharge their contents into the groove. It commences at the junction of fin and groove, and here it is partially enclosed in a chitinous framework; it gradually becomes smaller and finer as the tip of the spine is approached, to the apex of which it does not reach for a variable distance, usually about one-eighth of an inch or more.