MERCURIAL DIURETICS

INTOLERANCE AS SHOWN BY SKIN SENSITIVITY

BY

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The rarity of adverse effects following the use of mercurial diuretics is remarkable, considering how widely they are now employed. Many regular recipients with heart failure and, less frequently, with renal œdema would at least be confined to their beds but for these preparations. The causes of the few complications reported have been uncertain and idiosyncrasy or allergy has often been given as an explanation. Having seen many cases who receive doses of this drug with impunity for years, the temptation is to dismiss the explanation of simple accumulation. A hitch in a standard regime, however slight, is often interpreted as a contra-indication of the further use of a drug, although the cause of the untoward effect is not known. Such an abandonment in the case of mercurial diuretics frequently leads to a deterioration of the patient's health, and a fuller understanding of such reactions is therefore important.

Wolf (1931) reported a case of sudden death following intravenous salyrgan in a child aged four, with nephrosis; the injection preceding the fatal one caused a chill, fever, a morbilliform rash, and anorexia; but resulted in satisfactory diuresis although previously the output had been disappointing. Keith (1936) stated that injections of organic mercury might be followed by stomatitis, diffuse dermatitis, diarrhoea, hæmaturia, and renal insufficiency, but considered that these reactions were rare. He also noted that if the mercurial diuretics were discontinued for about ten days the drug could often be given again with satisfactory results. Klein and Seymour (1942) discussed several cases with skin reactions. In one, urticaria appeared after eight consecutive injections at unstated intervals, and an evanescent erythema followed the final two injections in this case. A transient erythema was seen in others, one of which after further salyrgan injections developed an "inflammatory reaction of the skin which progressed to a typical exfoliative dermatitis." In their opinion these cutaneous manifestations were warnings of more serious reactions to follow, and contra-indicated further use of the drug. A discussion of cutaneous eruptions produced by mercurial diuretics with many references is to be found under the names of De Graff and Nadler (1942). Types of reactions so produced include urticaria, small reddish spots or purpuric areas, and morbilliform or scarlatinaform erythemata; occasionally the rash was followed by desquamation in one to three weeks. They suggested that positive patch tests indicated an allergic basis and that although an accumulation was seen with the older type of mercurial diuretic, it did not occur with the rapidly excreted theophylline-containing mercurials. They also pointed out that an erythematous skin eruption may follow either the first or any subsequent injection of the diuretic. Relationship to dosage or excretive response was, however, not considered. Other theories have been suggested. According to Lesser (1888) peripheral vasodilatation is caused by the paralysing effect of mercury on the sympathetic nerves. The histological studies of Almkvist (1922) also indicate the cutaneous capillary dilatation is caused by mercury. Their studies of the reactions produced by mercurial diuretics in a woman, aged 27, with rheumatic heart disease were reported by Fox, Gold, and Leon (1942). Several mercurial preparations were found to affect her similarly and their experiments showed that the xanthine content of these substances was not to blame.

Engel (1937) quoted by Barber (1938) stated that novurit suppositories "should not be given at an interval of less than five days. Adherence to this rule renders the patient tolerant

of repetitive suppositories over a period of years without the production of a chronic inflammatory reaction in the rectal mucosa." This statement suggests that frequent application of the mercurial may lead to sensitization. Barber considers that signs of mercurial poisoning are "a sequel to failure of elimination when, as sometimes happens, diuresis does not occur." The effects which manifest themselves include stomatitis, diarrhoea, vomiting, hæmaturia, and purpura. Evans and Perry (1943) mention skin rashes caused by mercurial diuretics but do not associate them as forerunners of more serious things. Other authors have commented on the freedom of this treatment from serious complications (Evans and Paxon, 1941). We report the following new cases of skin erythema following the administration of mercurial diuretics.

CASE REPORTS

Case 1. A trolley bus conductor, aged 48, had essential hypertension with heart failure. Dyspnoea on exertion and nocturnal asthma started in 1942, and oedema of the legs in November 1943; from that time onwards he received from his private doctor 2 c.c. of neptal intravenously, three times a week with a good but diminishing diuretic response. In February 1944 a faint generalized pink rash with irritation was noticed, which steadily increased with each injection. He was then referred to one of us (A.B.). A positive patch test to neptal confirmed the suspicion that the rash was caused by that drug. A control test on a student was negative. The use of neptal was accordingly discontinued and the rash gradually faded. The patient's symptoms of cardiac failure, however, soon returned. By June, nocturnal dyspnoea was severe and so neptal was given again in doses of 2 c.c. twice a week. No recurrence of the rash or irritation took place. From July 1944 until his death in December, he was under our observation. Apart from a weakly positive result in August, patch tests frequently repeated, proved negative, as did similar tests to other organic mercurials including mersalyl, esidrone, and salyrgan. Although severe failure rendered necessary the use of frequent mercurials, neptal 2 c.c. every third or fourth day, and rest in hospital, the original dosage of 6 c.c. in a week was not employed from February 1944 onwards, and the diuretic response was excellent varying from three to four pints. It would appear that this man could tolerate 4 c.c. of neptal weekly as long as his elimination was satisfactory, but that 6 c.c. in a week over a period of 3 months with less efficient diuresis led to accumulation and skin manifestations. After a rest of three months, but without any active desensitization he showed no reactions to further injections and only a faintly positive patch test on one occasion.

Case 2. A woman, aged 39, was first admitted to hospital with nephritis (Type II, Ellis, 1942) in January 1943. Oedema of the nephrotic type was gross. The blood pressure was 180/100. There was no heart failure. The urine was loaded with albumin. The blood area was normal, and the plasma protein 4.6 mg. per 100 c.c. Rest, limitation of fluids, and a high protein diet did not alter the plasma protein and the oedema remained. Neptal, 2 c.c. intramuscularly was therefore started on February 22, 1944 and given every fourth day preceded by 30 grains of ammonium chloride by mouth. The diuretic response was disappointing and seldom exceeded 50 oz. This dosage was continued until May 1943 when the oedema of her legs which had persisted, increased greatly. She was therefore rested once more as an inpatient and the effect of 3 c.c. neptal intramuscularly was observed. At four daily intervals three such injections did not meet with proportionate outflow, and so the dosage was returned to 2 c.c. twice weekly, while she attended as an outpatient. Readmission was again necessary in October 1943. Her oedema was worse and her plasma protein still low (4 mg.). The hæmoglobin was 104 per cent. Within two months she had lost one stone in weight. Before her discharge on December 24, 1943 the dose of neptal was increased to 2.5 c.c. twice weekly with improved but only moderate response. This dosage was continued from outpatients until February 26, 1944 when an injection was followed by a generalized itching with erythema, mainly of the upper limbs and thighs. On March 6, mersalyl 2 c.c. was substituted, but this again produced itching and enhanced the rash. Mercurial dermatitis being suspected, a patch test of neptal (full strength) with saline control was carried out and this was positive when observed after 48 hours. The diffuse rash was now dry, fine, scaling, and less pink. After mercurials had been discontinued for two months, a further patch test was found to be negative. Salyrgan 2 c.c. was tried on May 4, this only produced an output of 2 pints but there was no skin reaction. She returned to neptal 2 c.c. twice weekly but the injection on May 13 was followed four hours later by a return of the itching rash, which spread up to the arms from the wrists. Within the next 48 hours a slight recurrence was also noticed on the neck and thighs. The rash was red to pale pink, punctate, macular, and sometimes confluent. Dry scaling patches up to 0.5 cm. diameter in both antecubital fossæ dated from the previous rash was much more severe. Her output to the last injection produced 60, 56, and 38 oz. on consecutive days, during a daily intake of 30 oz.

Three days after that injection her blood count showed an eosinophilia of 5 per cent which might have indicated an allergic reaction. A patch test that same day was uncertain, as some redness was caused even by the control owing to the irritable state of her skin. Ten days after that injection, the rash was coarser, and more powdery, involving upper limbs, buttocks, thighs, and neck. Itching was still intense. By June 6, the rash had spread down to the legs although improvement was apparent

elsewhere. The most severe areas, the inner side of the forearms, then received 100 r unscreened X-rays with marked benefit, and this was followed one week later by similar dosage to the outer aspect of the arms. By July 4 the rash had nearly gone; patch tests to 25 per cent solutions of neptal, mersalyl, salyrgan, and esidrone with saline control were applied and these were all still negative after three days. Full strength patches of these mercurials applied on July 17 were also negative. Her skin had therefore become negative to patch testing in just over two months from the last injection of neptal, although no desensitizing doses had been employed. From July 18 at weekly intervals other mercurial diuretics were injected including esidrone 1 c.c., mersalyl 2 c.c., and salyrgan 2 c.c., and no skin reaction occurred. Finally neptal was again used with satisfactory effect in 2 c.c. dosage at weekly intervals, from August to September when a patch test was again negative. An improvement occurred in her condition at this time. The œdema diminished rapidly, and no further mercurials have been required.

It would appear that this patient tolerated 2 c.c. neptal twice weekly for ten months without any adverse effect in spite of poor diuresis, but after eight weeks of 5 c.c. instead of 4 c.c. in each week, a rash appeared. After two months without injections, she could tolerate further mercurials for a time, and her patch test was negative. The second skin reaction took six weeks to clear completely, and by this time she was again patch test negative.

Case 3. A woman, aged 63, was first seen in June 1943 suffering from hypertensive heart failure and auricular fibrillation. The blood pressure was 210/130 and there was aortic valve disease. Besides digitalis and reduced fluid intake, her treatment included weekly intramuscular injections of 2 c.c. of neptal. Although the diuretic response was not satisfactory, improvement was maintained until eight months later when she complained of intense generalized itching of the skin with a weeping rash of the thighs and arms. Neptal was discontinued and her skin condition cleared. As the œdema returned, Guy's pill (powered squill, digitalis, calomel, gr. i) was given three times daily. After two weeks the patient noticed a recurrence of the rash on her left thigh and this spread rapidly to form a band about six inches wide almost encircling the limb. Soon the generalized itching returned, it was therefore decided that the Guy's pill, containing mercury to which she was apparently susceptible, must be discontinued in favour of tab. digitalis folia. The skin condition improved immediately, but the œdema increased. Three further doses of Guy's pill caused an exacerbation of the rash, which confirmed the observation that oral administration of the mercury was to be blamed.

Four months later the patient was again seen in consultation. Her ascites and œdema were gross, a patch test to neptal was negative. Mercurial diuretics were not again tried until late in November 1944 when 1 c.c. neptal resulted in a urinary output of 83 oz. Subsequent doses at long intervals were not followed by cutaneous complications.

Case 4. This man, aged 58, was first seen in consultation in April 1944. Ten years previously he had undergone subtotal thyroidectomy and now showed evidence of hypothyroidism. The history and cardiogram also suggested a cardiac infarction one year previously. The blood pressure, 115/105, which rose to 230/170 under observation, breathlessness, œdema of ankles, and pulmonary congestion provided evidence of heart failure. Commencing on April 19, 1944 he received 2 c.c. neptal intramuscularly twice a week for 3 weeks, then once a week until June 14, 1944 after which injections were given every fortnight. His urinary output was not recorded but, satisfactory at the start, it diminished latterly. On August 1 he developed a diffuse rash over his abdomen, thighs, and the outer aspects of the arm. Intense itching accompanied the rash which was worse a few days after the injection. A neptal patch test was positive when removed after three days, an irritating erythema underlying the gauze square. His wife who was acting as control showed a completely negative result. Neptal injections were then recommenced once a month with satisfactory diuresis and no return of the cutaneous complication.

Although the injections were infrequent compared with those received by some other cases, possibly accumulation of mercury occurred because the diuresis after each dose was insufficient to ensure elimination. The individual tendency of such a patient to sensitization, however, must be taken into consideration.

Case 5. A woman, aged 53, was admitted to hospital with mitral stenosis, auricular fibrillation, and chronic heart failure. One week later, as her improvement with rest, adequate digitalization, and reduced fluid intake was not satisfactory mercurial diuretics were started. The first injection, 2 c.c. neptal intramuscularly, produced a diuresis of 104 oz. and a diminishing but satisfactory output continued over the next few days. On the third day after the first injection, neptal was repeated, this time producing 122 oz. in the subsequent 24 hours, with marked clinical improvement. After a further five days a third dose only gave a response of 68 oz. and about 1½ hours after this she vomited and complained of generalized itching. No rash was seen although a careful watch was kept. Owing to an oversight the mercurial diuretics were not discontinued, and three days later a fourth injection of 2 c.c. neptal caused a similar irritation without a rash. A patch test applied after a lapse of three days showed a faint erythema with pin head vesicles; a control of saline was negative, as well as a neptal patch applied to a patient not receiving mercurials.

As the third injection met with a fair response only, a longer interval might have been allowed to elapse before the next injection. Itching of the skin too should have been sufficient warning that accumulation of the drug and sensitization of the skin were occurring.

Case 6. A man, aged 21, was admitted with heart failure and auricular fibrillation from mitral stenosis and aortic incompetence with stenosis. As the liver reached the umbilicus and ascites was starting without much peripheral oedema, congestive cirrhosis of the liver was suspected. Neptal intramuscularly in 2 c.c. doses twice a week had met with satisfactory diuresis from three weeks until one day before admission, when the last injection by the private doctor had proved inefficient. After admission and four days after the last mercurial, the same dose was given intravenously after pre-medication with ammonium chloride, with good diuresis. The injection of October 12, 1944 gave a response of 6 pints; but on the 16th no diuresis resulted. The next day the patient was drowsy, incontinent, with generalized oedema including the face, but with no orthopnoea. A diffuse blotchy pale pink rash had developed on the anterior aspect of the trunk, but no mention of itching was made at that time by the patient, possibly because of his mental torpor. Twitching of muscles, a blood urea of 140 mg. and an increase in albumin with a strongly positive guaiacum reaction in the urine, told of acute nephritis which was attributed to the mercurial treatment. The blood pressure, previously varying from 140/50 to 150/70 rose to 200/100 on October 13, and fell to the previous level after four days. A neptal patch test on the arm was then negative as were scratch tests, but a second patch test applied on the 19th in the scapular region was positive.

Normal rhythm was regained on October 19 and the patient's general condition improved. On that date, however, three days after the unsuccessful injection, the rash was more pronounced, particularly on the abdomen. The face was less puffy, and cerebation was clearer, but the breath was foetid owing to stomatitis. During the next week the rash gradually faded. The urinary output equalled the intake (30 oz.) and the albuminuria diminished. Subsequently the nephritic element improved rapidly, and from the 25th the urine was reported clear. Oedema was still gross in spite of improving output, and so on October 29 a patch test to neptal having been found negative, 1 c.c. was given intramuscularly. This met with an excellent response. The trunk was now almost clear of rash which, however, still remained in a maculo-papular form on the extremities. On November 3, 36 hours after a further intramuscular injection (2 c.c. neptal) a papulo-erythematous rash recurred over the extremities and trunk with great itching. A patch test again proved positive. Eight days later, another neptal injection was tried with entirely satisfactory results and no untoward effects. The rash was now fading but scaling. Oedema of the lumbar region was still gross. Subsequently the use of neptal was continued intramuscularly at weekly intervals, and patch tests were always negative before each injection. The diuretic response varied between 90 and 130 oz. Ascites required paracentesis although peripheral and pulmonary oedema was controlled satisfactorily considering the severe degree of cardiac failure. Recently a trial of Guy's pill, one thrice daily, was made without effect, and was discontinued after five days. At the end of this trial course 2 c.c. neptal produced a diuresis of 186 oz. and a patch test to neptal was negative.

The mercurial preparation not only showed the presence of sensitization in this case, but also produced stomatitis and probably an acute nephritic reaction. All these ill effects were overcome by reduced dosage and careful administration of the drug. Had neptal been abandoned, it is doubtful whether this patient would have left his bed; as it was, he led a quiet life as an out-patient until a sudden decline at the end of April 1945. All excess fluid was eliminated satisfactorily, except the ascites, caused by hepatic cirrhosis for which occasional tapping was required.

Case 7. A male, aged 47, was admitted under the care of Dr. Horace Evans in December 1941. He was a case of insidious nephritis (Type II, Ellis, 1942). A left nephrectomy had been performed in 1922 for renal tuberculosis. His renal efficiency tests showed slight impairment (blood urea 50 mg. per 100 c.c.) In January 1942 before his discharge he received one injection of neptal 2 c.c. intramuscularly with a response of 102 oz. (intake 48 oz.). He was under observation as an out-patient with a varying oedema of the ankles but received no further mercurial injections until January 1944. Two injections at an interval of one week were then followed by the administration of neptal tablets by mouth, the dose of which was 2 t.i.d. for two days in each week, after a preliminary trial of 1 t.i.d. on the first occasion. This dosage was continued until March 15 when it was noted that the tablets caused "a lot of acid" and retching. The intramuscular preparation was therefore recommenced instead of the tablets. Oedema was now increasing steadily. On April 5 the urinary output was 5 pints and his blood urea 48 mg. per 100 c.c. The diuretic response to neptal continued to be satisfactory, reaching 10 pints on May 13 and 4 pints on June 14. On July 26 an itching of the skin was treated by calamine lotion, but neptal continued in the previous dosage (2 c.c. weekly) until he was referred to one of us (A.B.) on September 6. There was a generalized symmetrical rash and oedema of his legs was slight, so it was recommended that mercurial diuretics should be omitted. On October 5 the rash was fading well, and patch tests which unfortunately had been previously omitted, were now negative both on the arms and at the site of the injection (buttock).

In spite of some degree of renal insufficiency, mercurials had been well tolerated from January until July 1944, although it is likely that renal impairment led to an accumulation of mercury over several months. The persistent oedema required the continuation of this regime, and, in the light of our experience since this investigation started, this patient would probably have continued to tolerate mercurial treatment had the interval between the doses been increased.

Case 8. A male, aged 54, was admitted with hypertensive heart failure on January 19, 1945 (B.P. 200/140). His urine was clear, and his blood urea was 58 mg. Oedema was extensive in the lumbar region and lower limbs. Cardiograms supported the diagnosis of hypertension without coronary obstruction.

His first neptal, 2 c.c. intramuscularly on January 25 was followed by a urinary output of 90 oz. Two days later a similar dose produced no diuresis, but output exceeded the fluid intake of 30 oz. by 12, 32, and 30 oz. on that and the subsequent two days. Two days after the second injection, he complained of generalized itching. His blood urea then was 62 mg. and his B.P. 160/90. As his oedema was increasing and a left pleural effusion had developed, neptal was given on January 31. Within three hours of this a morbiliform rash was noticed over his trunk and limbs. The urinary output that day only exceeded intake by a few ounces, and next day rectal incontinence disturbed the fluid measurement. No satisfactory diuresis resulted. A patch test applied 44 hours after the onset of the rash, was negative in 24 hours, but positive in 48 hours. The patient became worse and died on February 7. At autopsy there was no evidence of nephritis and signs of hypertensive heart failure were present.

Case 9. A retired clergyman, aged 83, was admitted to another hospital in August 1944 with coronary thrombosis. Three weeks later oedema slowly developed. From September 2, 1944, mersalyl 1 c.c. was given intramuscularly at weekly intervals. The diuretic response varied from 80 to 100 oz. in the 24 hours and the fluid intake was about 2 pints. Although oedema was not gross, it persisted in spite of prolonged rest and other adjuvants such as digitalis. From October 28 mersalyl 1 c.c. was injected twice weekly, and the urinary output was recorded as between 60 and 84 oz. but for one poor response of 30. During this period the fluid intake was 35–40 oz. daily. The next two injections within one week were of mersalyl in 2 c.c. dosage, and these resulted in 58 and 62 oz. in the following 24-hour periods. From November 4 the mercurial employed was neptal 2 c.c. intramuscularly twice in a week, with diuretic measurements varying between 55 and 107 oz., averaging 78, for the next nine weeks.

In January 1945 the patient's condition was much the same, but he had left bundle branch block. Neptal was continued twice weekly, preceded by three doses of 15 grains of ammonium chloride. The urinary response was recorded as varying between 40 and 100 oz. in the 24 hours, the average output being 59 oz. During that period of five weeks the fluid intake was variable, sometimes reaching 50 oz., and on one occasion 4 pints, although generally being less than 40 oz. From February 12 the injections were given somewhat irregularly, on February 19 and 21, on March 1, 9, 13, 16, 20, and 23. The diuretic response during this period varied between 55 and 66, averaging 58 oz., the daily fluid intake was fairly constant at 35 oz. and without neptal the output was 30 oz. in 24 hours.

On the day after the last injection, an erythema was noticed on the patient's feet, legs, and back. This rash was accompanied by itching and slight diarrhoea. A patch test applied three days later was found to be positive after 48 hours. His urine, usually clear, contained a cloud of albumin with granular and hyaline casts and gave a positive guaiacum reaction on March 27, but was again reported albumin free a few days later. An X-ray of his chest on March 29 showed enlargement of the left ventricle but no hilar congestion. The blood urea on April 6 was 60 mg. per 100 c.c., his blood count was later reported as 3,980,000 red cells and Hb. 80 per cent, and his plasma protein 5.4 (albumin/globulin ratio 1.7).

After a negative patch test, one further dose of 2 c.c. of neptal was given, eleven days after the last injection. There was no diuretic response (output 30 oz.), neither was there any recurrence of rash, albuminuria, or diarrhoea.

It was obvious from these investigations that the oedema was not now caused by heart failure, although initially it may have been so. The falling diuretic response to continued frequent injections of mercurial seemed to assist accumulation of the metal, and skin sensitization.

DISCUSSION

Many patients with sustained high dosage show no signs of intolerance to mercurial diuretics; in fact, the incidence of such manifestations is rare. Numerous patients with heart failure receive full doses of neptal once or twice a week for periods of two or three years without the slightest ill effect. On the other hand, a few cases that have been reported show immediate acute sensitization to mercury, as mentioned by De Graffe and Nadler (1942). Sundaram reported sudden death in a boy of ten years with rheumatic heart disease after the first injection (0.5 c.c. salyrgan in 10 c.c. saline intravenously), but it is not yet proved that such accidents are allergic in nature.

Sensitization, idiosyncrasy, or allergy may be of different degrees. In one of our cases (Case 6) a severe skin reaction was accompanied by manifestations of an acute nephritic nature and by stomatitis. The other eight who received mercurial diuretics only gave the skin signs. It is therefore suggested that rashes and itching are evidence of a moderate degree of sensitization and might be followed by grosser complications if administration of the drug is unscientifically continued.

A positive patch test is a sign of idiosyncrasy or allergy and is accepted as such by practically all the leading authorities. According to Sulzberger (1933), "whenever a reaction of eczematous character is produced at the site of the application of the patch, provided a

substance has been used that is not a primary irritant" (presumably, in the strength employed) "one may conclude that eczematous hypersensitiveness of the skin to this substance has been demonstrated." Patients who have received mercurials for many months or years without any symptoms related to the skin have in our experience shown negative patch tests without exception. There is as yet no evidence that patients exhibiting cutaneous manifestations of intolerance are patch test negative before starting treatment. A routine patch test in a series of cases before injections are started, would decide this point; but, although primary idiosyncrasy has been reported, it is expected that such initial investigations would support the theory of acquired sensitization in the majority of cases. There would appear to be a threshold of concentration of mercury in the blood below which no signs of allergy are given, but above it they are positive. One of the earliest works on sensitization to drugs was by Jadassohn of Breslau, *A Contribution to the Study of Dermatoses Produced by Drugs* (Translation, 1900). It pays much attention to the cutaneous complications of mercurial treatment. In the main, little changes have occurred in the principles underlying the phenomenon of sensitization set out in that work, reference to which proves of great interest in this present problem; for instance, "the remarkable fact already confirmed from observation on the action of mercury and other remedies, that at first a certain cumulative action was necessary to bring out, so to speak, the idiosyncrasy . . ." Similarly, Bloch, quoted by Goldsmith (1936) wrote "idiosyncrasy is only a relative term depending not only upon the nature of the substance but also on its concentration." That accumulation of the drug in the body precedes skin sensitization, as suggested by Barber (1938), seems likely from the consideration of our own cases which tend to show a common factor, namely deficient elimination compared with the amount of drug administered. This may be caused by high or too frequent dosage, as in Cases 1, 2, 5, and 9, and assisted by renal impairment from long standing nephritic damage as in Cases 2 and 7 or from congestive changes as in Case 8, and possibly in Cases 3 and 4. Prolonged administration naturally must tend to produce accumulation of the drug; although with good diuretic response and suitable dosage it is our experience that this factor alone seldom leads to sensitization from the mercurial diuretics. The degree of susceptibility, however, must vary with each patient; for instance, in Case 6 although the previous injection had produced 120 oz. of urine and the patient was still grossly œdematous, the next injection caused an allergic reaction affecting the skin, kidneys, and mouth. Also, we have as yet no conclusive evidence that a good diuretic response assists the elimination of mercury. Quantitative estimations of this substance in the blood and urine are desirable.

From our observations it would appear that sensitivity, as shown by patch testing, may be lost after a brief period of rest from the drug and without desensitizing doses. This fact was noted by Jadassohn who remarked "cases are reported that seem to prove that idiosyncrasies may disappear in the same way as they have been acquired." Goldsmith (1936) was also of this opinion and he wrote "phases occur in specific super-sensitiveness in which the exhibition of allergen no longer causes any material effect." That transient conditions, such as threshold concentration and renal impairment, play a part is also suggested by this author's comment that "allergic disorders depend on other factors, often temporary ones, besides specific sensitization." So far, we have not met the patient who required desensitizing doses of mercury such as those employed by Tate and Klorfajn (1944) with sulphonamides.

Sensitization of one tissue to a substance contained in the body is not necessarily accompanied by a similar condition in other tissues. In our investigation we have employed the patch method of testing for cutaneous sensitivity. Our technique has been as follows. A small square of gauze dressing, about one inch wide and four or five layers thick, is soaked in the test solution (full strength neptal supplied for intramuscular injection) excess of which is expressed. This patch is placed on the skin, and covered by a larger square of dry lint, the two then being held in position by a still larger piece of elastoplast. Thus if the adhesive substance causes any irritation, the resulting cutaneous change will not be contiguous with the central square of positive reaction but separated from it by a normal area protected by lint.

It will be seen from our case reports that a positive patch test was not always obtained at the onset of itching or a rash. Case 6 exhibited a negative reaction on the arm to a patch

applied 24 hours after the onset of the abdominal rash although a positive was produced in the scapular region 48 hours later. Perhaps this observation may have been the result of a technical error. In all the other cases tested, a positive patch test followed the cutaneous symptom although such tests often became negative before the skin was clear.

The patch test would seem to have a useful application, in the treatment of patients with heart failure by mercurial diuretics. In no patient under our observation has an injection of a mercurial diuretic caused a rash when a patch test immediately preceding it proved negative. Accordingly this test should be useful when accumulation of the drug is suspected or when continuation of treatment is desirable after cutaneous sensitization.

In conclusion, it is suggested that cutaneous sensitization to mercury need not contraindicate the subsequent employment of these diuretics in adjusted dosage after a short interval.

SUMMARY

Nine cases of skin reactions to mercurial diuretics are presented.

Many patients with sustained high dosage show no signs of intolerance to mercurial diuretics.

Sensitization, idiosyncrasy, or allergy may be of different degrees. Skin rashes and itching without other complications would seem to indicate moderate sensitivity.

There would appear to be a threshold concentration of mercury in the blood, above which signs of allergy develop, and this may vary with the individual patient.

Accumulation of the drug is assisted by excessive dosage, poor diuresis, and renal impairment.

The patch test is useful in determining the presence of sensitivity of the skin, especially when accumulation of the drug is suspected or when continuation of treatment is desirable after cutaneous sensitization.

The occurrence of cutaneous complications does not preclude further use of mercurial diuretics in adjusted dosage once the phase of sensitization is past.

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