limited to those which inhibit autonomic activity, because of their greater theoretical interest and promise for the future, as compared with drugs which produce autonomic stimulation. The sympathetic stimulators such as adrenaline and its derivatives, and the parasympathetic stimulators such as eserine and mecholyl have established therapeutic indications and uses which have not changed materially in recent years.

No attempt has been made to gloss over the serious shortcomings of all the presently available autonomic blocking agents, but search for new drugs of this type is being carried on in a very wide and fertile field, and there are excellent grounds for the hope that new compounds will be developed to fulfill Dr. Mark Nickerson's criteria, namely: high specificity of site of action, prolonged effectiveness by oral administration even against strong autonomic stimuli, and a wide margin of safety between the therapeutic and the toxic dosage.

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CEREBRAL THROMBOSIS FOLLOWING MERCURIAL DIURESIS

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THE PATIENT in congestive heart failure is prone to develop venous thrombosis, often followed by embolism which may prove fatal. Slowing and stagnation of the circulation favour these undesirable events. It has however been observed that such complications occur with greater frequency following the institution of treatment to correct the heart failure.[1] This led to theories that digitalis or mercurials had specific effects hastening the coagulation of blood. Current opinion does not accept this view, but postulates that hæmoconcentration and other changes due to the diuresis *per se* are the cause of the increased tendency to thrombosis at this time.

While peripheral, cardiac, and pulmonary thrombi are reported as occurring with frequency following diuresis, little mention is made of cerebral thrombosis. The writer has noted only one article in the literature available to him. This was a report by Russek and Zohman[2] in 1949, recording three such events. The paucity of reports may be due to the frequent difficulty of differentiating cerebral emboli from thrombi. More probably it is because such a complication may be considered as fortuitous, the possibility that the thrombosis was precipitated by the treatment not being considered.

The following report is that of a patient who developed cerebral thrombosis immediately following a single injection of mercuhydrin. The possibility that this may have been merely a coincidence cannot of course be eliminated, but but because recent investigations indicate that thrombotic phenomena in general may follow diuresis it is felt to be worthwhile reporting.

CASE REPORT

The patient, a 64 year old white male, was admitted to the hospital on October 11, 1951. Six days prior to admission he had developed anorexia, nausea, abdominal cramps, and slight looseness of the bowels. These symptoms were also experienced by other members of the household. The night previous to admission he had become short of breath and had to sit up all night for that reason.

Three years before, during a "check up" he had been told that he had a heart condition, although he felt well at the time. One and a half years previous to the present illness he was treated in hospital for congestive heart failure, the symptoms and findings being identical with those of the present admission. He had remained well after discharge with a normal cardiac rhythm, until the present episode.

On examination he was a well nourished man in mild respiratory distress. The neck veins were distended two inches above the clavicle in the sitting position. Fundi showed a grade 2 sclerosis. The heart was moderately enlarged, the apex being palpated 5 inches from the midline. No murmurs were heard. Rapid auricular fibrillation was present, (heart rate 165, pulse rate 80). Blood pressure was 153/100. A few crepitations were heard in the lungs. The liver was felt 2 fingerbreadths below the costal margin. There was no abdominal tenderness or mass felt. Grade i pitting œdema of legs was present. Rectal examination was negative.

Urinalysis showed plus one albumin with a few casts. Chest x-ray revealed moderate cardiac hypertrophy. The electrocardiogram was interpreted as showing auricular fibrillation and ischæmic changes compatible with

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coronary disease, but with no evidence of recent infarction.

The relationship of the gastro-intestinal symptoms to the cardiac condition was not clear. The former may have been due to gastric and intestinal congestion, but it was considered more likely that he had primarily a gastro-intestinal upset, which induced fibrillation followed by failure in a diseased heart.

The patient was treated by diet, digitalis, and later quinidine. The digestive symptoms and dyspnœa cleared and the rhythm reverted to normal in a few days. The pulse however, remained somewhat fast and he still had some œdema. Mercuhydrin, 1 c.c., was ordered, and this was given intramuscularly on October 17. A good diuresis resulted with a decrease in weight of five pounds.

When visited the following day the patient appeared listless, drowsy, and somewhat confused. This was attributed to dehydration, although a possible renal impairment was thought of. The urinary output and specific gravity however, appeared adequate. A blood urea nitrogen was 28 mgm. per 100 c.c., an increase from 22 mgm. % a few days previously. The patient was encouraged to drink fluids, and a B.U.N. on October 20 was again reported as 22 mgm. %.

The mental state remained unchanged, and the reason became apparent on October 20, when he complained of weakness of his left thumb. Examination showed almost complete lack of power in this digit, but no other motor impairment could be demonstrated. There was also found a Horner's syndrome on the left, absent abdominal reflexes, and an upgoing toe on the left. These were the only abnormal findings elicited. It was felt that the patient must have two lesions,—right cortical and brain stem thrombi. On the following day the process showed extension, evidenced by the appearance of a left facial paresis. A stellate block was considered at this time, but was thought inadvisable by a consulting neurosurgeon.* No further extension of the lesion occurred, the patient's sensorium cleared, and there was gradual improvement in the neurological findings. He was discharged November 8.

COMMENT

The mercurial diuretics are among our most valuable drugs, and it is not the purpose of this report to detract from their usefulness. However there is practically no potent drug which may not have undesirable effects at times, and the mercurials are no exception. When indicated we do not hesitate to digitalize the patient, being on the alert for toxic effects, and the same attitude should be observed with the use of diuretic measures.

Untoward reactions of mercurials which are due to hypersensitivity or mercurial poisoning have long been recognized, but are of rare occurrence. The disturbances due to rapid dehydration are of greater importance, and the incidence of these has no doubt increased since we have added the low sodium diet, and more latterly the resins to our armamentarium.

TOXIC EFFECTS OF THE MERCURIALS

Sudden deaths.—A review of the literature in 1948[3] collected reports of 32 cases of sudden death. All fatalities followed intravenous injection and were attributed to sudden ventricular fibrillation or asystole. The authors of the report recommended therefore that mercurials should be administered routinely by the intramuscular route, the intravenous method being reserved for cases who did not respond well to intramuscular therapy.

Allergic reactions[4] are uncommon. Chills with fever and vomiting, urticaria, and asthmatic reactions have been reported. These effects are specific for the organic radicle, and should they occur, substitution of a different mercurial is required.

Mercurialism was not uncommon when the first injectable mercurial (novasurol) was introduced. With later preparations such complications have been rare, and have occurred usually when the drug has been pushed in the absence of effective diuresis, in the presence of renal damage, or of pre-existing stomatitis or colitis. Untoward reactions reported have included stomatitis, colitis, purpura, and toxic nephrosis. The use of the drug during active (acute or subacute) nephritis, may result in anuria. Chronic nephritis is a relative contraindication, since the presence of cardiac failure may require its cautious use.

Redigitalization may occur in the already fully digitalized patient. The release of digitalis from œdema fluids may be accompanied by evidence of digitalis toxicity.

Acute prostatic retention.—The rapid bladder filling during diuresis may precipitate prostatic retention and require use of a retention catheter.

Dehydration[5] is commonly seen in regimens having as their objective the attainment of "dry weight", that is, the maximum weight loss attainable. Since mercurials can cause diuresis and weight loss in normal individuals, such a goal would appear unphysiological. Recent opinion inclines to the view that such measures are not conducive to optimum well being, and may aggravate latent renal disease.

Electrolyte depletion.[6 to 9]—There is much current interest and investigation of this problem, which is no doubt occurring with greater frequency since we have learned of the importance of salt in the pathogenesis of œdema, and improved our methods of excreting it from the body. The action of the mercurials of course is to inhibit salt resorption from the renal tubules. When combined with low salt diets, and more

*Dr. Dwight Parkinson.

latterly the resins, excessive excretion of electrolytes may occur. It must be emphasized that such depletion may develop while œdema is still present,—so that the anorexia, nausea, lassitude muscular pains, and even coma which follow may erroneously be attributed to the congestive failure,—and treatment be pushed when it should be modified. The loss of chlorides is initially in excess of sodium, with hypochloræmia and alkalosis as the first manifestation. Failure of diuresis after mercurial injection usually occurs at this time. The administration of ammonium chloride for two days prior to an injection is therefore good practice. This drug should be given intermittently as continuous use may cause acidosis.

Sodium depletion is a later and more serious development. The depleted extracellular fluid becomes hypotonic. It is presumed that in order to maintain osmotic balance with the intracellular fluids, water shifts into the cells which become overhydrated. Symptoms are produced of "water intoxication". It is thought that hydræmia of the renal cells is the cause of the impaired kidney function, oliguria and finally azotæmia which may occur. Biochemical tests will reveal a low plasma sodium, chlorides below 97 m.e.q. per litre, and a rising B.U.N. When recognized, diuretics must be discontinued and salt allowed. In severe cases hypertonic salt solutions have to be given intravenously.

Thromboembolic phenomena. — Marvel and Shullenberger[1] carefully studied a group of patients in congestive failure during the initial stages of treatment. Evidence of venous thrombosis developed in 25% during the first 10 days. In all these cases there was active diuresis, accompanied by hæmoconcentration and usually an increase in prothrombin activity. When thrombosis occurred it did so when these changes were at their peak. On the basis of their findings and that of other authorities, the authors suggest that intensive methods of therapy be reserved for critical cases. It has been common practice, irrespective of the urgency of the case, to digitalize rapidly, prescribe a salt free diet, and administer mercurials when initiating treatment. The results are usually dramatic initially, but at times, especially in the elderly patient, the later course may not be as satisfying. The writer recalls the observations made to students on the wards by the chief of the medical service,* "I see quite a few elderly patients admitted who have been managing to get along fairly well with their congestive failure. They are quickly wrung dry with all the best treatment and not infrequently are followed to the autopsy room." A slower approach, gradual digitalization, and the use of the diuretics when digitalis is found inadequate is a safer regimen in the average case.

Batterman[10] studied a large number of patients with congestive failure, and came to the conclusion that rest alone can clear up 60% of them. Eighty per cent of the remainder will respond to digitalis, leaving only about 7% in whom the use of diuretics is mandatory.

"Complete bed rest" prescribed for heart failure unfortunately predisposes to thrombosis. Free movement of limbs should be encouraged. Samuel Levine[11] encourages his patients, in the absence of shock or severe chest pain, to rest in a comfortable chair. He believes this lessens the work of the heart and reduces the frequency of thrombosis.

The success of anticoagulants in the treatment of myocardial infarction has led to similar investigation of their use in heart failure. It may be recalled that a study of nearly 1,000 well controlled cases of infarction showed a reduction in mortality of one-third, due to a lesser incidence of thromboembolic complications.[12]

A number of less extensive studies have been carried out on the use of anticoagulants in heart failure.[13] The results reported from three medical centres,[14, 15, 16] are in complete agreement. The combined figures of the three groups are as follows:

TABLE I.

	Controls	*Anticoagulant treated*
No. of cases	350	427
Deaths	15.7%	8.0%
Deaths not due to thrombosis	8.3%	7.3%
Thromboembolic deaths	7.4%	0.7%

The mortality in these series was, as seen, reduced by one-half in the anticoagulant-treated cases, by the virtual elimination of thromboembolic complications.

When administering anticoagulants to these patients it must be recalled that impaired hepatic function is frequent in congestive failure and the prothrombin time may be low to begin with.[17] It has been stated that this does not contraindicate the use of the anticoagulants in these cases,[18] but that preliminary prothrombin estima-

*Dr. J. D. Adamson.

tions and strict laboratory control are essential. Dosage requirements are usually less in these patients.

SUMMARY AND CONCLUSIONS

A case of cerebral thrombosis following the administration of a mercurial diuretic is reported. While this may have been coincidental, it is pertinent that recent studies indicate thrombotic phenomena are more prone to occur in congestive failure following initiation of diuresis. Hæmoconcentration and prothrombin increase predispose to these complications. Where time permits a gradual rather than intensive plan of treatment, while less dramatic, may be a safer method of management. There is good evidence that anticoagulant therapy is effective in reducing thromboembolic complications with their attendant mortality during the early treatment of congestive heart failure.

A brief summary is also given of other reported untoward effects of mercurials.

In conclusion it is again emphasized that mercurials are valuable and often indispensable for our treatment of heart failure, but undesirable effects may occur and we should be alert to recognize their occurrence.

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THE PROBLEM OF PENICILLIN RESISTANT STAPHYLOCOCCAL INFECTION*

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AN INCREASING NUMBER of reports from all parts of the world concerning the prevalence of penicillin resistant staphylococci are appearing in the medical literature. Spink and co-workers[1] in 1944 reported 12% of 68 strains to be penicillin resistant. Gallardo,[2] Plow,[3] Bondi and Dietz[4] in 1945 all reported a similarly low incidence of penicillin resistant strains. Barber[5] in 1948 reported that the incidence of penicillin resistant strains in her studies was 14% in 1946; 38% in 1947 and 58% in 1948. From these reports and others it is apparent that this ubiquitous organism has a peculiar faculty for adaptation to the influence of noxious agents in the environment. Further it appears from the work of Barber *et al.*[6] (1948 and 1949) and others that an increasing number of the penicillin resistant strains are being isolated from institutional infections. These workers have also shown that staphylococci isolated from widely separated hospitals in England belong mainly to two particular phage groups. It is suggested from their work that a particular strain, having a high resistance to penicillin is propagated in hospitals by cross infection.

The nasal carrier rate for pathogenic staphylococci is known to vary considerably and amongst the general population a carrier rate of 30 to 50% can usually be expected, McFarlane,[7] 1939, Cunliffe,[8] 1949. Various authors including Barber,[6] 1949, Voureka and Hughes,[9] 1949, Rowntree and Thompson,[10] 1949 have shown that these organisms are predominantly penicillin sensitive. Forbes[11] has shown that these "wild staphylococci", isolated from clinical infections outside the hospital are usually more sensitive to penicillin than those isolated from hospital patients.

It has been suggested that intimate contact with a hospital environment may affect the carrier rate in hospital workers. Recently this has been the subject of study by Rowntree and Barbour[32] in Australia. They reported that student nurses, within a period of 5 weeks from beginning ward duty, showed an increased staphylococcal nasal carrier rate from 52.6 to 71.4%. The number carrying penicillin resistant strains rose during the same period from 4.3 to 32.1%. Those nurses whose cultures were in-

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