NEUROCHEMISTRY AND NEUROCHEMISTS*

BY

JOHN N. CUMINGS

From the Department of Chemical Pathology, Institute of Neurology, the National Hospital, Queen Square, London

A presidential address to a learned society or the inaugural address of a professor is usually devoted to one of three possible themes. It can be concerned with political considerations, with a historical survey of some subject, or it can be devoted to a purely scientific problem.

We, in our Association, have had in the past two of these themes, the political and the scientific. I am suggesting combining a historical approach with a scientific theme in relation to neurochemistry, and hope to show how in this century progress has been made in this particular field and how there can now be offered applications of the methods, techniques, and theories of the pure neurochemists to clinical medicine and neurology. Therefore the object is rather to show how basic research has frequently been of value at a later date in an understanding of disease processes and subsequently in the treatment of disease. Occasionally this order has had to be reversed and this will also be illustrated.

During the first 50 years of this decade there were 59 medical and physiological Nobel prize winners, and of these some 10 were biochemists or used biochemical methods in the field of neurology. Hence one in every six of all these Nobel prize winners was interested in the field which is under discussion, and some of these workers will be mentioned.

The chemistry of the nervous system can be said to have begun with Thudichum. He was born in Büdingen in Germany in 1828, and died of a cerebral haemorrhage in London in the year 1901. He qualified medically in 1851 at the University of Giessen, but had many other interests, one of which was singing, especially the singing of Italian arias. He was attracted to Liebg, thereby making his entry into the field of chemistry. However, like so many others, he had to flee the country of his birth, and, coming to England, he married in 1854 Charlotte Dupré, a sister of a chemist at the Westminster Hospital Medical School. He discovered urochrome in 1864, and suggested the name “lutein” for a certain colouring matter in animal tissues, a name later changed to lipochrome. His work on the chemistry of the brain took place during the years 1865 to 1882, and many substances that we now know much more about, such as sphingomyelin, kerasin, and cerebroside acid, were described and named by him subsequent to their preparation and identification. He measured the specific gravity of brain and also commented on the presence of such substances as copper in the brain. His monumental treatise, Physiological Chemistry of the Brain, appeared in London in 1884. Later in life, after he had retired, he turned his attention to food and wine, about which he wrote in 1895 and 1896.

As a direct result of his work a chemical section of the Kaiser Wilhelm Institute was started in Munich in 1928 largely through the activity of Kraepelin, who had been the first to devise a useful classification of schizophrenia. The name of Thudichum is remembered in another way, for I have discovered that in Galesburg in the state of Illinois, U.S.A., a psychiatric research department has named its laboratory after him. It might be worth mentioning now that this Thudichum laboratory, under the direction of Dr. Harold E. Himwich, is the chief psychiatric biochemical research centre in that state, and had officially given to it in 1957 a year’s income of some £6,000 more than it is reported our Government gave for psychiatric research for the whole of Great Britain.

Another milestone was reached in 1937 when Page, then in New York, but later in Cleveland, published the volume entitled Chemistry of the Brain. He had worked earlier in Germany and knew many of Germany’s prominent biochemists.

The subject of neurochemistry has now expanded well beyond the recognition of these earlier workers, and any general review of the subject is quite obviously impracticable. I have, therefore, chosen only a few major topics to discuss.

*The Presidential Address delivered to the Association of Clinical Pathologists on October 2, 1959.
**Oxidative and Carbohydrate Metabolism**

The brain has been shown to have a high rate of oxygen utilization. In fact, about 25% of the total oxygen used by the body in basal conditions is utilized by the brain, as was shown relatively recently in 1948 by Kety and Schmidt.

The brain makes use of glucose almost exclusively in its metabolism in contrast to other organs, and by sampling the arterial and the jugular venous blood it has been shown that the respiratory quotient is for practical purposes unity. Naturally, alterations in degrees of consciousness produce some alterations in utilization, and Himwich has made extensive investigations along these lines, and his and other authors' work is discussed in his book entitled *Brain Metabolism and Cerebral Disorders*.

Oxygen uptake varies from one tissue to another, the order of activity increasing from peripheral nerve to white matter to cerebral cortex. In the same way the trigeminal nucleus has a relatively low activity.

The method by which glucose is metabolized in the brain is very similar to that in other body tissues, following the pathway glucose-6-phosphate, fructose-6-phosphate, and fructose-1,6-diphosphate to 2 molecules of triosephosphate, and finally to pyruvate. There is then a conversion of pyruvate to a 2 C compound which by a complex reaction can enter the citric acid cycle, which has a close connexion with the Krebs cycle.

These basic portions of chemical knowledge, which are related to all body structures, had been obtained by pure chemists such as Krebs, a Nobel prize winner in 1953. Hans Adolph Krebs was born in Germany at Hildesheim some 59 years ago. After studying medicine he went to Berlin and then returned to Freiberg in Professor Thannhauser's clinic. He left Germany and came to Cambridge from whence he went to Sheffield and then to Oxford. In Cambridge in 1933 he worked on the synthesis of glutamine from glutamic acid and ammonia, while it was from Sheffield in 1937 that he published his work on the citric acid cycle. The tricarboxylic acid cycle is now recognized as the major pathway for the oxidation of carbon compounds in the body generally. However, unlike other tissues, the cerebral metabolism of available carbohydrate is not dependent on any local action of insulin. The work of Krebs embodies earlier theories of such workers as Szent-Györgyi and Martius and Lopp. Szent-Györgyi won his Nobel prize in 1937. He was born in Budapest in 1893 and qualified in 1917. However, he began research work as a first-year medical student. After a chequered career he finally became Director for the Institute of Muscle Research at Woods Hole, Massachusetts, where he is at present working.

I must mention two other workers in this field of basic science; Carl and Gerty Cori, both born in Prague in 1896, eventually emigrating to America. They married in 1920, but had collaborated in research as class mates earlier. Their work, for which they were joint Nobel prize winners in 1947, was in relationship to glycogen, an important compound in carbohydrate metabolism.

I will mention very briefly the application of some of these various studies in so far as they affect us as practising clinical pathologists.

John P. Peters was born in 1887 and died in 1955. He was 34 years at Yale, and during that time he applied the biochemistry of carbohydrates to clinical medicine mainly in the fields of disorders of metabolism and more especially to diabetes. He is a joint author of the very well-known book *Quantitative Clinical Chemistry*.

Another person interested in carbohydrate metabolism who must be mentioned is Sir Rudolph Peters, who qualified in medicine in 1915, and after the first world war went to Cambridge and worked with Gowland Hopkins. In 1923 Hopkins offered Peters the chair of biochemistry at Oxford, where the laboratory had been started 18 months earlier by Benjamin Moore, who had been the occupant of the chair of biochemistry at Liverpool, the first ever to be created in England. Here at Oxford at the age of 33, Peters continued his pioneer studies, and much of his earlier work was on oxidation and the SH compounds. This followed investigations by Warburg and by Meyerhof, two very eminent German chemists.

Much of the work of Peters was on thiamine, and few others were interested in this subject at that time. He is now investigating new problems of the monofluorocarbon compounds in relation to vitamin deficiency.

One of the pupils of Peters is Thompson, who, while at Oxford with Peters, together with Stocken, developed during the last war 2,3-dimercaptoopropanol, now known as dimercaprol (B.A.L.). This compound, as is well known, acts as a remover from the body of many heavy metals, including lead and copper. Thompson and Peters were interested in pyruvate metabolism; the pyruvate oxidation system contains highly reactive thiol (SH) groups. Arsenicals combine
with these groups and pyruvate metabolism is thereby impaired. Coenzyme A also contains one of these essential SH groups, and this is the site at which B.A.L. competes, thereby offsetting the action of poisonous substances such as the arsenicals. More recently, Thompson has applied these principles to the question of peripheral neuritis and polyneuritis in man, and he has shown that in a percentage of cases of polyneuritis the fasting blood pyruvate level may be raised, and further that there is an abnormal rise in blood pyruvate after a test dose of glucose. He has shown further that, in a proportion of the patients who show this abnormal pyruvate tolerance test, vitamin B\(_2\) used therapeutically is able to effect some degree of cure of the patient and the blood levels of pyruvate may return to normal.

**Cerebral Lipids**

The brain contains some 12% to 15% by wet weight of lipid, or 50% to 60% by dry weight. This fatty material was found by Thudichum to consist largely of cholesterol, sphingomyelin, and cerebroside. Neutral fat is also present but in very small quantities. The early workers used whole human brain and separated the substances on a macro basis with characterization of the component constituents. Thierfelder, for instance, at the beginning of this century, isolated one of the cerebrosides (cerebron), and 50 years later Chatagnon in Paris, by fresh experimental methods, obtained a substance which gave crystalline appearances and infra-red spectroscopic findings which were similar to those of Thierfelder’s original preparation, which was still in existence and with which it was compared.

It is perhaps correct to state that the largest amount of work done on these substances in the human brain has taken place in the last 10 years. Nevertheless, in the 1920s Klenk, Remkamp, Deuel, and others were separating and characterizing many of these compounds on a purely chemical basis. Considering very briefly one or two compounds, one can say that Gmelin in 1826 found that cholesterol in the brain had the same formula and configuration as cholesterol in gall-stones, but it was later found that the esterified form of cholesterol did not exist in any appreciable amount in normal brain tissue.

Sphingomyelin, so named by Thudichum, was later found to contain a fatty acid which is probably the C\(_{24}\) lignoceric acid, but it may also be stearic or nervonic acid. Sphingomyelin is closely related to cerebroside as can be seen in Fig. 1, from which it can be observed that sphingosine is a component part of not only sphingomyelin and cerebroside but also of ganglioside and possibly of a substance called cephalin B.

Klenk and his co-workers around 1940 found a compound in the brain which they named substance X, later renamed ganglioside, and it was shown that it contained neuraminic acid, hexosamine—probably a galactosamine—and a hexose radicle. There is still a good deal of controversy about the exact composition of ganglioside, for slightly varying views from those of Klenk have been expressed by both Svennerholm and Bogoch in the last two years. Klenk is a pure chemist and has built up at Cologne a famous department full of enthusiastic workers who are, however, also interested in disease processes.

Thannhauser and his colleagues in recent years have made important contributions to the chemistry of sphingomyelin and of the plasmalogens, originally described by Feulgen in muscle. He has had much to do with work on various diseases, such as Gaucher’s disease and xanthomatosis, while working in America.

The school in Canada led by Rossiter had investigated the brains of normal infants and adults, estimating the relative amounts of sphingomyelin, cerebroside, cholesterol, and lecithin found in the white and grey matter, and their results have been confirmed by Brante in Sweden and also by the group working with me, all within the past 10 years. Just recently, we have been able to add, in an even more extensive series, the results of similar estimations of the various lipids in brains from the foetus, the full-term infant, the young infant, and the child.

![Sphingolipid diagram](https://example.com/sphingolipid-diagram.png)

**FIG. 1.—The sphingolipids.**
Proteolipid is an important part of the myelin sheath, and Finean has represented the myelin sheath as being made up of alternate layers of lipid and of protein.

Recently a study has been carried out on the water-soluble proteins of the brain. Portions of cerebral white matter in 5 to 10 g. amounts were extracted with 10 to 20 ml. of 10% sucrose, and similar amounts of cerebral cortex extracted with 5 to 10 ml. quantities of sucrose. The extracts were concentrated, and the proteins present examined by starch electrophoresis. Different areas of the brain have been selected, and so far nine portions of the frontal lobe, seven from the parietal, and 10 from the occipital lobe have been examined with some slight differences in pattern being observed. The results are illustrated in Figs. 2 and 3. The patterns found do not appear to bear any relation to the proteins of the serum, which in some instances were put up in parallel with the brain extracts.

Interesting results, however, have been obtained in cases of suspected cerebral oedema. A well-
marked band of protein has been demonstrated in the same region that albumin appears in a serum pattern in starch electrophoresis (Figs. 4 and 5). This albumin band has been found even in portions of brain which on naked-eye examination were not definitely oedematous. Macroscopic diagnosis of cerebral oedema is notoriously difficult as has been shown previously by histological examination as well as by chemical techniques, and this method appears to be a delicate one for its demonstration.

Much work has been done on the amino-acid composition of the various proteins, and Richter in England and Waelsch in America have worked extensively on this subject. Amino-acids are being metabolized continuously as has been shown by isotope studies, and some of them, such as glutamic acid, play a very important part in general metabolic processes, as was mentioned earlier when discussing the work of Krebs.

Brain tissue contains both glutamic acid and its amide glutamine. There is no evidence to suggest that glutamic acid can replace glucose as a source of fuel. It can react with ammonia to form glutamine or be oxidized by glutamic dehydrogenase with the formation of ammonia. The later stages of such a cycle include $\alpha$-ketoglutaric acid, and this has a connexion with the Krebs cycle. It has been suggested that some of these pathways may be involved in hepatic coma.

Returning now to the lipids, the next links in the chain that should be considered are the experiments in 1948 on Wallerian degeneration by the group led by Rossiter. They cut the sciatic nerve in animals and at various stages of degeneration examined chemically the distal part of the nerve as well as control nerves. It was found that at first water increased in amount while total phospholipids decreased. Neutral fat decreased but later returned to normal levels.
The components of myelin—sphingomyelin, cerebroside, and free cholesterol—decreased, but esterified cholesterol from being absent in the intact and normal nerve increased appreciably. Proteins, probably proteolipid or neurokeratin, also decreased. Here then was experimental evidence relating to demyelination. Recent papers by this group have been concerned with various associated enzyme changes.

Some workers have applied these techniques to the various disease processes. It has, for instance, been shown in work which I did in 1953 that demyelination in multiple sclerosis followed a chemical pattern which in many ways was very similar to that found in the cut sciatic nerve. There is in multiple sclerosis in the active plaques, but not in chronic lesions, an increase of water and a loss of the myelin lipids, together with a well-marked increase in esterified cholesterol.

One of Klenk's pupils, Dr. Debuch, has shown that a substance, lysocephalin, possesses some properties similar to those of lysolecithin. It has been suggested that this might well produce demyelination locally within the myelin sheath, and this type of enzymic action has been proposed as a possible cause of demyelination in multiple sclerosis. Thompson and his colleagues are pursuing this aspect.

Very similar lipid chemical findings have been obtained in Schilder's disease or the so-called sudanophilic type of diffuse sclerosis. It has not yet been possible to demonstrate the factor that causes this demyelination, whether in fact it is enzymic in nature and whether it also has a genetic basis. The results that have been obtained in both multiple sclerosis and sudanophilic diffuse sclerosis are illustrated in Tables I and II, where it will be seen that there is a very great increase in the amount of esterified cholesterol, and this is absolutely characteristic of these two diseases. The deposition of esterified cholesterol in histological sections stained by Scharlach R stain red, as can be seen in Fig. 6.

Turning very briefly to the group of diseases known as the lipidoses, there is abundant evidence from the work of Thannhauser, Klenk, and my own group that some of the various substances which have been described by the chemists are increased in amount in these diseases. Thannhauser and his associates found in Niemann-Pick's disease affecting the peripheral organs that there was an increased content of sphingomyelin in these organs, and Klenk and I have both shown in patients in whom the nervous system is involved that there is an increased content of sphingomyelin and of cholesterol in the brain itself. We have also found an increased amount of ganglioside in the cerebral cortex.

In amaurotic family idiocy Klenk and his associates in 1942 obtained raised levels of ganglioside in the brains of patients, and they found that the level of neuraminic acid, that is of ganglioside, showed an increase of even as much as five to 10 times the normal, and this increase occurred almost exclusively in the cerebral cortex where the ganglion cells can be seen by histology to be full of a P.A.S.-positive material.

During the past few years the application of these basic chemical facts has been used in clinical pathology in the field of neurology. Chemical investigations of the brains of patients dying from multiple sclerosis, from lipidoses, and from encephalitis have been made by me, and distinctive patterns obtained in these different diseases. This knowledge has been utilized in the examination of cerebral biopsy material. Numerous patients with progressive mental disturbances have been examined by clinicians without a definite diagnosis being possible, although some of the conditions are known to be familial. After all the facts have been given to the parents and permission obtained, a small sample of cerebral tissue, about 1 cm. cube, was removed. My histological colleagues have shared these pieces of tissue with me, and I have examined some 74 such specimens. A positive diagnosis has been made on 51 occasions by chemical examination, and in only one case have the histological and biochemical opinions been in
complete disagreement. It is not possible to give the complete details, but one or two examples will demonstrate the type of findings that have been obtained. (I must mention that no clinical defect has resulted, nor have we been able as yet to obtain post-mortem confirmation of our opinions, apart from three cases, and these patients died more than six months after operation.)

A patient with a diagnosis of amaurotic family idiocy arrived at histologically and chemically showed typical histological lesions in the cerebral cortex, and these can be seen in Figs. 7 and 8. The chemical examination revealed a marked increase of ganglioside in the absence of any evident loss of phospholipid or of demyelination (Table III).

### Table III

**Cerebral Lipids in Biopsy Specimens from Amaurotic Family Idiocy**

<table>
<thead>
<tr>
<th></th>
<th>Cerebral White</th>
<th>Cerebral Cortex</th>
<th>Normal Cortex</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total phospholipid</td>
<td>5-88</td>
<td>3-70</td>
<td>3-5-4-5</td>
</tr>
<tr>
<td>Total cholesterol</td>
<td>3-41</td>
<td>1-11</td>
<td>1-0-1-5</td>
</tr>
<tr>
<td>Esterified</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Hexosamine</td>
<td>0-36</td>
<td>0-70</td>
<td>0-5-0-7</td>
</tr>
<tr>
<td>Ganglioside</td>
<td>0</td>
<td>2-3</td>
<td>1-0-1-5</td>
</tr>
<tr>
<td>Water</td>
<td>75-1%</td>
<td>81-9%</td>
<td>82-85%</td>
</tr>
</tbody>
</table>

Results in g./100 g. fresh tissue except ganglioside and hexosamine, which are in g./100 g. dry tissue.

Metachromatic leucodystrophy, which is familial, shows an altered appearance of the myelin pattern, for in the white matter there is metachromasia as illustrated in Fig. 9, while the chemical findings are seen in Table IV. It is to be noted that there is a marked increase of hexosamine in the white matter, while there is also evidence of a moderate degree of demyelination.

### Table IV

**Cerebral Lipids in Biopsy Specimens of Metachromatic Leucodystrophy**

<table>
<thead>
<tr>
<th></th>
<th>Cerebral White</th>
<th>Cerebral Cortex</th>
<th>Normal White</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total phospholipid</td>
<td>1-32</td>
<td>3-77</td>
<td>7-0-8-0</td>
</tr>
<tr>
<td>Total cholesterol</td>
<td>1-28</td>
<td>0-93</td>
<td>4-0-5-0</td>
</tr>
<tr>
<td>Esterified</td>
<td>0-11</td>
<td>0-14</td>
<td>0</td>
</tr>
<tr>
<td>Hexosamine</td>
<td>0-48</td>
<td>0-74</td>
<td>0-2</td>
</tr>
<tr>
<td>Ganglioside</td>
<td>0-36</td>
<td>1-4</td>
<td>0</td>
</tr>
<tr>
<td>Water</td>
<td>81-0%</td>
<td>83-3%</td>
<td>70-74%</td>
</tr>
</tbody>
</table>

Results in g./100 g. fresh tissue except ganglioside and hexosamine, which are in g./100 g. dry tissue.

It must be mentioned that metachromatic deposits occur in the kidney, and examination of the urine reveals such metachromatic material, and this was indeed found in this patient.

Lastly, subacute encephalitis of the inclusion body or Van Bogaert type shows some slight but definite chemical findings, and are shown in Table V. There is only slight demyelination without the presence of cholesterol ester but with a slight increase in hexosamine levels.

### Table V

**Cerebral Lipids in Biopsy Specimens of Subacute Encephalitis**

<table>
<thead>
<tr>
<th></th>
<th>White</th>
<th>Cortex</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total phospholipid</td>
<td>5-4</td>
<td>4-0</td>
</tr>
<tr>
<td>Total cholesterol</td>
<td>2-7</td>
<td>1-2</td>
</tr>
<tr>
<td>Esterified</td>
<td>0-05</td>
<td>0-02</td>
</tr>
<tr>
<td>Hexosamine</td>
<td>0-51</td>
<td>0-63</td>
</tr>
<tr>
<td>Ganglioside</td>
<td>1-0</td>
<td>1-0</td>
</tr>
<tr>
<td>Water</td>
<td>77-5%</td>
<td>81-1%</td>
</tr>
</tbody>
</table>

Results in g./100 g. fresh tissue except ganglioside and hexosamine, which are in g./100 g. dry tissue.

Table VI shows the actual number of cases which have been examined chemically, and the groups of diseases into which they fall.

### Table VI

**74 Cerebral Biopsies Examined Chemically**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Abnormality Diagnostic</th>
<th>Abnormal but Not Diagnostic</th>
<th>No Abnormality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>10</td>
<td>5</td>
<td>26</td>
</tr>
<tr>
<td>Amaurotic family idiocy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metachromatic leucodystrophy</td>
<td>9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Multiple sclerosis</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sudanophilic diffuse sclerosis</td>
<td>4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subacute encephalitis</td>
<td>6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Organic dementia</td>
<td></td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>1</td>
<td>4</td>
<td></td>
</tr>
</tbody>
</table>

### Acetylcholine

Hunt and Taveau in 1906 were the first to demonstrate that acetylation of choline (a substance known to Thudichum and obtained originally from phosphatide in bile, hence its name) resulted in a product of greatly increased pharmacological activity. Loewi demonstrated in 1921 that liberation of a substance now known as acetylcholine, but called by him "Vagusstoff," was present in the perfusing fluid of a frog's heart after stimulation of the vagus nerve. Sir Henry Dale in 1914, 1929, and 1933 very ably described the various effects of acetylcholine, and in the last paper of 1933 introduced the terms "cholinergic" and "adrenergic." Loewi and Dale shared the Nobel prize in 1936. In 1911 Dale, in association with Barger, was the first to isolate histamine from animal tissues. However, he is best known for his work on acetylcholine, which was later followed by work on neostigmine. Considerable knowledge is now available.
concerning the synthesis and destruction of acetylcholine after its release at nerve endings and the conception of an acetylcholine cycle has been put forward. It was soon clear from experimental procedures that an enzyme must be present to convert acetylcholine into some less active form. Such an enzyme, cholinesterase, which has been found to be widely distributed in the body, can in fact break down acetylcholine to acetic acid and choline. Two main types of such an enzyme have been found and these have been called, in 1943, true and false cholinesterase, or specific or non-specific cholinesterase. Nachmansohn, who proposed the latter term in 1945, was also an able worker on acetylcholine.

These two cholinesterases have been found to act on different substrates, and are present in varying amounts in different organs and areas. True cholinesterase was found by Nachmansohn in 1939 to be located more in the cerebral cortex than in the cerebral white matter, while pseudo-cholinesterase was present to a greater extent in the white matter, as in fact was shown by Ord and Thompson in 1952.

After release of acetylcholine at the nerve endings and its hydrolysis some process must then be present for its resynthesis. Quastel and his co-workers in 1936 suggested such a process, and it has since been proved that acetylcoenzyme A provides the acetyl group which is transferred to choline by the action of the enzyme choline acetylase. Acetyl-coenzyme A is probably derived from pyruvate, which links this mechanism, therefore, with the glucose cycle.

Only one or two applications of these findings to clinical neurology will be mentioned. Much biochemical work on epilepsy has been done at Montreal led by Elliott. Elliott and Tower in 1952 estimated bound acetylcholine and cholinesterase in normal portions of brain and in epileptogenic areas of brain, and found that in the latter there was a marked reduction of bound acetylcholine. Further work both by Elliott in Montreal and by Tower in Bethesda has followed, but it is too early to state its final practical value. Elliott has recently reported on $\gamma$-amino-butyric acid which is present in brain tissue, and has said that both glutamate and $\gamma$-amino-butyric acid may be “action substances” of neuropsychiological importance, and that from his experimental results there may be a balance of effects of these two substances, and that they may determine neuronal activity.

The other condition I wish to mention is ginger paralysis. This is a form of motor neuritis first seen in the United States in 1930 following the drinking of a beverage containing an extract of Jamaica ginger. This was later found to contain tri-ortho-cresyl phosphate (T.O.C.P.). Various degenerative lesions were found in axis cylinders and in the myelin sheath in not only the peripheral neuritis mentioned but also after poisoning by T.O.C.P. present in other substances such as apioi and in certain cooking oils. The hen can be used as an experimental animal, and work has been done since 1950 on this subject by a number of experimenters. Earl and Thompson in 1952 showed that T.O.C.P. was a selective inhibitor of pseudocholinesterase in nervous tissue and in plasma but that true cholinesterase was unaffected. Certain new organophosphorus insecticides are also similarly dangerous, for parathion and mipafox both cause plasma and erythrocyte cholinesterases to be lowered. These last compounds do not, however, produce paralysis or degenerative lesions of nerve.

It is perhaps of interest to notice here that amongst some of these substances recently produced is one for locust control, and experimental work on this has just been published showing the effect of such substances on cholinesterases in the nerve cells of locusts.

So far an attempt has been made to show that our understanding of disease processes has followed a fairly definite pattern, and has stemmed from basic chemical work. Application of such basic knowledge has been applied to suitable patients with varying diseases in order to elucidate the cause and the nature of the pathological lesion involved. However, we now come to a group of disorders in which the reverse procedure has been followed. In patients with some diseases, abnormal chemical findings were first discovered, and, following this, basic chemical knowledge had to be determined. In 1908 Sir Archibald Garrod delivered the Croonian lectures at the Royal College of Physicians and his subject was “Inborn Errors of Metabolism.” There are now known to be a number of such disorders, and one or two of them will be mentioned and an indication as to how progress has been made in our knowledge of these diseases.

In 1934 Fölling found in certain imbeciles in Oslo that there was an excess in the urine of a substance, phenylpyruvic acid. He detected this with the use of a weak ferric chloride solution. It was soon found that the disease, phenylketonuria, was associated with a rare recessive gene in homozygous form. Various physical differences from the normal are present in these children as well as a varying degree of mental impairment. The patients are often blonde, the stature and
Fig. 6.—Sudanophilic diffuse sclerosis. Scharlach R, × 40.

Fig. 7.—Amaurotic family idiocy. P.A.S., × 400.

Fig. 8.—Amaurotic family idiocy. Scharlach R, × 400.

Fig. 9.—Metachromatic leucodystrophy. Toluidine blue, × 40.
head measurements may be reduced, and temperamentally they are docile. The sweat may also be excessive and contain phenylpyruvic acid.

Having discovered a chemical abnormality in the patient, other workers in the past decade proceeded to determine the metabolic pathways that could be involved to produce this abnormality. The fundamental disorder appears to be that the inborn error is one concerned with a failure to metabolize phenylalanine along the normal pathways. In the normal subject phenylalanine is changed in the body into tyrosine by means of an enzyme, phenylalanine hydroxylase. In the patient with this disease this step is not possible, and phenylalanine circulates in the blood and is disposed of as phenylpyruvic acid and phenyllactic acid. There also appears to be an abnormality involving indoles and tryptophane. An attempt has recently been made to treat these patients by dietary restriction of phenylalanine, but this should be done in the first few weeks of life. The patients are given a casein hydrolysate which is freed of phenylalanine, tyrosine, and tryptophane.

Acute porphyria is another condition in which abnormal metabolic pathways have been shown to exist by Rimington. This condition is sometimes associated with a polyneuritis, and I have had the opportunity of seeing and examining a number of such neurological patients.

The third condition I wish to mention is hepatolenticular degeneration, which is now regarded as due to an inborn error of metabolism, for this disease appears to be associated with a disordered copper metabolism. Again the initial observations were made in patients with this disease, for it was discovered by Rümpel that copper and silver appeared to be deposited in the tissues. Although this observation was made in 1913, and further observations along very similar lines were made in 1929 and 1930, it was not until an extensive investigation was made in 1948 that its full significance was appreciated. There is also a considerably increased urinary excretion of copper, and the blood level of copper is low. A substance, caeruloplasmin, which, it has been suggested, may act as a copper transporter, was shown in 1952 by Gitlin and Scheinberg to be absent or only present in minimal amounts in the blood. Two monographs have recently been written on this subject, so that it is obviously impossible to discuss it in full. Further, although some of the chemical abnormalities in the disease have been discovered, the actual mechanism which causes these changes had not yet been found. However, in 1948, as a result of the finding of increased copper deposition, a suggestion was made that B.A.L., a substance mentioned earlier, might be an effective form of therapy. This indeed is the case, for remissions of considerable periods of time have resulted from its use in many patients. Wilson considered that patients with this disease died within four to seven years after the onset of symptoms, and, although older patients have been known to live longer, the younger patients have died sooner. I have investigated 35 patients and personally treated 20 patients with B.A.L., and Table VII shows the results obtained. One of those treated is alive after eight years, and a number lived at least five years. As far as is known, two have married, and a few have been able to work again. Only two are known to have died, and each of these developed a severe cirrhosis of the liver; a portal caval shunt operation was performed and later both died in hepatic coma. The copper content of the liver in both cases, and the brain in one case, was within normal limits, thereby demonstrating the effectiveness of the treatment as far as the copper deposits were concerned. Neurologically, too, they were still improved before death, but the cirrhosis of the liver had advanced relentlessly.

This review is very incomplete, only a few subjects having been mentioned, but it may be that it demonstrates the evolving pattern of the biochemistry of the nervous system and the value of basic research when applied to clinical practice.